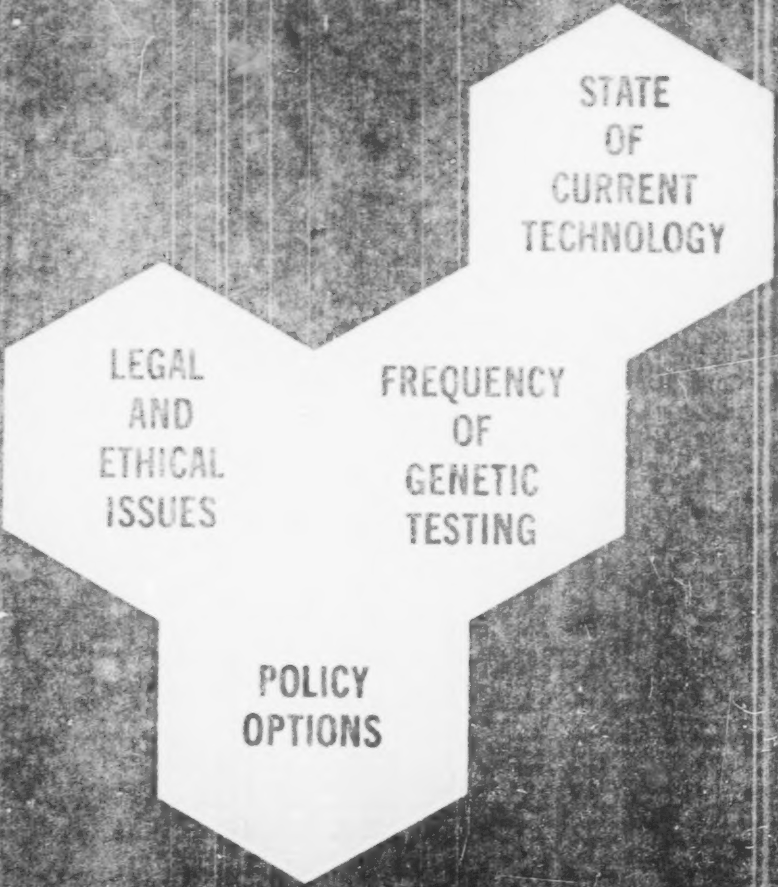
The Role of Genetic Testing in the Prevention of Occupational Disease



STATE
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ISSUES

FREQUENCY
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The Role of Genetic Testing in the Prevention of Occupational Disease

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Foreword

This report examines a technology, genetic testing, that may be useful in reducing occupational disease, but that also raises concerns about potential misuse. Genetic testing encompasses two major techniques, one (screening) that may be able to identify individual workers who are genetically at higher risk to disease; and another (monitoring) that may serve as an early warning system that exposure to a hazardous agent in the workplace has occurred. Information from these techniques might be used in various preventive measures, but some people fear it could result in workers being unfairly excluded from jobs.

OTA undertook the study at the request of the House Committee on Science and Technology. The study examines the technology and its social implications. It evaluates the evidence supporting its claimed benefits, the extent of testing, and how the results have been used. Social issues, particularly of a legal and ethical nature, are identified and discussed. Finally, congressional options for both promotion and control are presented.

In preparing this report, OTA consulted with members of the project advisory panel, with contractors and special consultants, and with numerous other experts in industry, academia, labor, medicine, law, economics, and ethics. Drafts of the final report were reviewed by the advisory panel chaired by Arthur Bloom and by approximately 32 other individuals and groups representing a wide range of disciplines and perspectives. We are grateful for their many contributions. As with all OTA reports, however, the content is the responsibility of the Office and does not constitute an endorsement by the advisory panel or the Technology Assessment Board.

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Glossary

Acetylation.—The introduction of one or more acetyl groups into an organic compound.

Allele.—One of several alternate forms of a gene.

Amino acid.—Any one of a class of organic chemical compounds characterized by the presence of an amino group (NH_2) and a carboxyl group (COOH) attached to either side of a central carbon atom. They are the primary building blocks of proteins; 20 major types are found.

Anemia.—A condition characterized by a decreased oxygen-carrying capacity of the red blood cells because of reduced number of cells, too little hemoglobin, or malfunctioning hemoglobin.

Assay.—Any technique that measures a biological response.

Biologically significant.—An exposure or dose that can cause detectable damage or disease.

Carcinogen/carcinogenesis.—An agent that induces cancer.

Carrier.—An individual apparently normal, but possessing a single copy of a recessive gene obscured by a dominant allele; a heterozygote.

Centromere.—A specialized region of a chromosome that holds the two chromatids together and that is involved in directing chromosome movements during cellular reproduction.

Chromatid.—One of the two daughter strands of a duplicated chromosome that is still joined by a single centromere.

Chromosomal aberration.—An abnormality of chromosome structure or number.

Chromosomes.—The structures in the cell nucleus that store and transmit genetic information.

Clastogen.—Chromosome-damaging agent.

Codominant.—Alleles are codominant if each is expressed independent of the presence of the other; the effects of expression are additive.

Cyanosis.—Slightly bluish, grayish, slatelike, or dark purple discoloration of the skin due to the presence of abnormal amounts of reduced hemoglobin in the blood.

Cytogenetics.—The study of the relationship of the microscopic appearance of the chromosomes and their behavior to the genotype and phenotype of the individual.

Deletion.—A chromosomal aberration involving the loss of a portion of a chromosome.

Deoxyribonucleic acid (DNA).—The genetic material of all cells.

Dominant.—An allele that exerts its phenotypic effect when present either in homozygous or heterozygous form.

Dose-response.—An increasing biological response with increasing dose of a chemical or ionizing radiation.

Dosimeter.—Device or methodology for measuring the dose of a chemical or ionizing radiation to a biological system.

Duplication.—A chromosomal aberration in which a portion of a chromosome is present more than once; may involve whole genes, parts of genes, or series of genes.

Endpoint.—The particular biological response being measured.

Erythrocyte.—Mature hemoglobin-rich red blood cell involved in oxygen transport.

Gene.—A unit of heredity. At present, genes are usually equated with units of function, that is, the sequence of DNA required to code for one polypeptide chain or one RNA molecule.

Genetic monitoring.—The periodic testing of workers to assess damage to their DNA or chromosomes from exposure to hazardous substances or agents.

Genetic predisposition.—Susceptibility to illness on the basis of one's inherited genetic constitution and triggered by an environmental stress.

Genetic screening.—A one-time test to determine the presence of particular genetic traits in individuals. For this report, the term is limited to the screening of workers for genetic traits that might cause them to be at increased risk for occupational disease.

Genetic tests.—Those tests that determine a person's genetic makeup or that identify changes (damage) in the genetic material of certain cells for the purpose of identifying people who may be at risk of disease when exposed to hazardous substances.

Genotoxic.—Damaging to the genetic material.

Genotype.—The genetic constitution of an organism (to be distinguished from its physical appearance or phenotype).

Germ cell.—The male and female reproductive cells; egg and sperm.

Hemoglobin.—Protein carrier of oxygen found in red blood cells. Composed of two pairs of polypeptide chains and an iron-containing heme group.

Hemolytic.—Pertinent to the breaking down of red blood cells.

Heterozygous.—Having different alleles at a genetic locus.

Homozygous.—Having indistinguishable alleles at a particular locus on both chromosomes.

Human leukocyte antigens (HLAs).—A set of immunologic proteins found on the surface of all cells; each person's set is thought to be as unique as fingerprints.

Hypoxia.—Result of lack of an adequate amount of oxygen in inspired air such as occurs at high altitudes; reduced oxygen content.

Initiation.—The first step in the development of cancer.

Inversion.—A chromosome rearrangement in which a central segment produced by two breaks is inverted prior to repair of the breaks.

In vitro.—Pertaining to experiments done in a cell-free system. The term is sometimes used to include the growth of cells from multicellular organisms under cell culture conditions.

In vivo.—Pertaining to experiments done in a system such that the organism remains intact, either at the level of the cell (for bacteria) or at the level of the whole organism (for animals).

Ionizing radiation.—High energy electromagnetic radiation, associated with gamma and X-rays, which is capable of changing the electronic structure of atoms.

Karyotype.—A chart made from a photograph of the chromosomes in which the homologous pairs are matched and arranged in numerical order from the longest to the shortest pair.

Leukocyte.—White blood cell.

Locus (pl.—loci).—The position of a gene on a chromosome.

Lymphocyte.—One of the major groups of white blood cells.

Messenger RNA (mRNA).—Type of RNA that carries the transcribed genetic code from the DNA to the protein-synthesizing enzymes to direct protein synthesis.

Mutagen/mutagenesis.—Any substance that damages the genetic material.

Nucleotide base.—Structural unit of nucleic acids.

Nucleus.—A relatively large spherical body inside a cell that contains the chromosomes in their uncoiled, threadlike state.

Oxidation.—Chemical reaction where there is a loss of electrons.

Phenotype.—Appearance or observable nature of an individual as determined by his or her genotype and the influence of the environment. Individuals that appear alike may be genetically different.

ppm.—parts per million.

Predictive value.—The likelihood that a person with a positive test result has the disease or that a person with a negative result does not have the disease. Also refers to the likelihood that the index or marker (chromosome damage) predicts the occurrence of a disease.

Promotion.—The second step in the development of cancer.

Protein.—A linear array of amino acids joined by peptide bonds. In their biologically active states, proteins are folded into specific three-dimensional structures and function as catalysts in metabolism and to some extent as structural elements of cells and tissues.

Recessive.—An allele which exerts its phenotypic effect only when present in homozygous form, otherwise being masked by the dominant allele.

Reduction.—Chemically, the acceptance of electrons; used as the opposite of oxidation.

Relative risk.—The ratio of the incidence of disease among exposed persons divided by the same rate among nonexposed persons.

Reliability.—The ability of the same specimen to give the same result repeatedly when measured by different laboratories or by different individuals in the same laboratory on several occasions.

Sensitivity.—The ability of a test to identify correctly those who have a disease.

Serum.—The liquid portion of the blood that carries the blood cells.

Somatic cell.—All cells of the body except the germ cells.

Specificity.—The ability of a test to identify correctly those who do not have the trait or disease which is being tested.

Teratogen/teratogenesis.—An agent that interferes with embryonic development.

Trait.—A distinguishing feature; a characteristic or property of an individual.

Transcription.—In gene function, the complementary copying of the genetic code from DNA to messenger RNA.

Translation.—In gene function, decoding the messenger RNA into an amino acid sequence in the production of a protein.

Translocation.—A chromosomal aberration in which a portion of one chromosome is attached to another chromosome; often a reciprocal exchange of segments between two chromosomes.

Validity.—The extent to which a test will correctly classify true susceptible and true nonsusceptible individuals; sensitivity and specificity are components of validity.

Part I

Introduction to Genetic Testing

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Chapter 1

Executive Summary

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Chapter 1

Executive Summary

Occupational illness and genetic testing

The problem of occupational illness

Occupational illness cost the U.S. economy over 850,000 workdays in 1981.* Diseases and other medical conditions associated with the workplace range from minor skin rashes to cancer. Some experts estimate that exposures to hazardous substances at work may play a role in 5 percent of all cancers. One substance—asbestos—is at the center of litigation over claimed illness that could result in insurance payments in the tens of billions of dollars over the next three or four decades. A large asbestos company has had more than 16,500 lawsuits filed against it and, as a result, has filed for reorganization under the Bankruptcy Act. Clearly, occupational illness has a serious and far-reaching impact not only on society as a whole but also on individuals who face impaired health and shortened lifespans.

What steps are being taken to mitigate this problem? Scientific and industrial response has varied: environmental and biological monitoring, engineering controls, personal protection devices, and modified work practices are among the techniques used today.

And on the horizon is an emerging technology —genetic testing—that may prove useful in reducing occupational disease, especially disease arising from exposure to two main workplace hazards: chemicals and ionizing radiation. That new technology—its potential applications and its limitations, its current state of development, and its legal, ethical, and social implications—is the subject of this report.

Genetic testing, as used in the workplace, encompasses two types of techniques. Genetic screening involves examining individuals for certain inherited genetic traits. Genetic monitoring involves examining individuals periodically for environmentally induced changes in the genetic material of certain cells in their bodies. The assumption underlying both types of procedures is that the traits or changes may predispose the individuals to occupational diseases. (Changes in the germ cells—egg and sperm—could result in birth defects in offspring but such reproductive effects are not part of this study.)

Although this technology is still in its infancy, it has the potential to play a role in the prevention of occupational diseases. It is technologically and economically impossible to lower the level of exposure to hazardous agents to zero. However, if individuals or groups who were predisposed to specific types of occupational illness could be identified, other preventive measures could be specifically directed at those persons. This is the promise of genetic testing. At the same time, however, the technology has potential drawbacks and problems. For example, the ability of the techniques to identify people who are predisposed to occupational illness has not been demonstrated. In addition, some people are concerned that its use could result in workers being unfairly excluded from jobs or in attention being directed away from efforts to reduce workplace hazards.

While it may be too soon to be able to answer many of the questions raised by genetic testing, it is not too soon for society to begin to consider them. The technology is developing, and some major companies have used it to a limited degree. Many more companies have expressed an interest in using it in the future. Moreover, genetic testing is one of a number of technologies that purport to identify people, both in and out of the workplace, who face an increased risk for disease. Policy decisions made on issues raised by genetic testing are likely to be relevant to the issues raised by those other technologies. Thus, the Committee on Science and Technology of the House of Representatives requested an assessment of genetic testing in the workplace.

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*The number of lost workdays is based on a survey by the Bureau of Labor Statistics, which acknowledges that the figure understates the amount of occupational illness because the survey does not adequately reflect chronic diseases and those with long latency periods.

Health hazards in the workplace

While there are many different kinds of hazardous substances or physical agents in the workplace, this report focuses on chemicals and ionizing radiation. It is for these two categories of hazards that genetic testing has been used and that some data exist for evaluating the scientific validity of such tests.

Virtually all chemicals are hazardous, if a person is exposed to a sufficient degree. Chemicals may be irritating, toxic, mutagenic, teratogenic, and/or carcinogenic. Moreover, the hazard of working with chemicals is compounded by the likelihood of multiple exposures to one or more chemicals over time. Exposure to more than one chemical may result in a synergistic effect—damage greater than the additive damage of the individual exposures.

The exact number of hazardous chemicals found in the American workplace is unknown. An Environmental Protection Agency (EPA) inventory lists more than 55,000 different chemicals in commerce, most of which are hazardous at sufficiently high exposure. Chemicals are found not only in companies that produce them but throughout the manufacturing sector. The National Institute for Occupational Safety and Health estimated that 8.9 million workers in the manufacturing sector were exposed to hazardous chemicals in 1980.

Photo credit: Office of Technology Assessment

Chemical manufacturing plants such as the one shown produce hazardous chemicals to which workers may be exposed

Ionizing radiation is energy in the form of waves or particles that produce certain charged particles in passing through matter. X-rays are a well-known example of ionizing radiation. This radiation can harm exposed individuals or their unborn children. For the exposed individual, the principal risk is that he or she may develop cancer. For unborn children, the principal risks are childhood leukemia and birth defects.

Occupational exposures to ionizing radiation (above natural background levels) occur in many fields, such as the health professions, nuclear fuel mining and production, industrial testing, and laboratory research. Estimates of the number of exposed workers have varied from 750,000 by the Committee on the Biological Effects of Ionizing Radiation to 1.1 million by EPA.

Photo credit: Department of Energy

Protective clothing worn by employees in nuclear power generating facilities to avoid radiation exposure

The use of genetic testing for the prevention of occupational disease

The problem of occupational diseases resulting from exposure to chemicals or ionizing radiation can be addressed in many ways. These include lowering exposure levels through engineering controls, physical and biological monitoring of exposure levels, medical screening and monitoring of workers, and individual protective devices. Genetic testing falls within the category of medical screening and monitoring.

THEORETICAL FOUNDATIONS

Genetically determined individuality is a fact of life. People differ not only in such obvious physical characteristics as height, facial features, and skin color, but also in ways that can be determined only in a laboratory, such as by blood type or types of proteins found in blood serum. Variations in some characteristics or traits result from the interaction of many genes; variations in other traits result from variations in a single gene that controls that trait. The probability of any two people (except identical twins) being exactly alike is astronomically small.

Genetic variability is also a factor in the differing reactions of people to environmental stresses, which include disease-causing agents such as bacteria, viruses, and chemicals. For example, some people have a deficiency in an enzyme called glucose-6-phosphate dehydrogenase (G-6-PD). The production of this enzyme is controlled by a single gene, and the deficiency is caused by a variant form of the gene. The deficiency usually is harmless. However, if these people take certain drugs for malaria or eat fava beans, they may suffer from acute anemia, due to the destruction of their red blood cells. Thus, G-6-PD deficient individuals are at a higher risk of illness than other people when exposed to those environmental stresses. Some scientists have postulated that people with G-6-PD deficiency may also be at increased risk of disease in workplaces where they are exposed to chemicals that are similar to the antimalarial drugs.

Many factors besides genetic makeup can cause an individual to be predisposed to illness from environmental stresses. Some of these are age, sex, preexisting illnesses, nutritional status, personal habits (such as smoking), and prior exposure to the environmental factors.

Prior exposure is particularly important for the purposes of this report. If the environmental factor is a chemical, it may be in the body at levels at which even slight additional amounts could cause illness. In fact, the prior exposure may already have begun the disease process even though the disease may not yet have manifested itself in overt symptoms.

These considerations lead to the concept in occupational medicine of unequal risk. People who differ according to age, sex, medical history, nutritional status, lifestyle, genetic makeup, or prior exposure to hazardous agents might differ in their risk for future illness when exposed to hazardous agents in the workplace. Some may be at increased risk; in other words, they might have a higher probability than others for developing a condition, illness, or other medically abnormal status. Theoretically, it should be possible to identify such people if the risk factors could be reliably identified and if the factors could be demonstrated scientifically to be correlated with an increased risk of disease. In some cases, however, depending on the disease mechanisms involved and the state of scientific knowledge, it might be possible only to identify groups at an increased risk of disease. In other words, the group as a whole might have a higher risk compared to other groups, but it would be impossible to predict which individuals in the increased risk group might develop the disease. Genetic testing is a collection of emerging techniques that may eventually permit the identification of individuals or groups at increased risk to certain occupational diseases.

DETECTION OF INCREASED RISK IN INDIVIDUALS OR GROUPS

The term genetic testing applies to several techniques used to examine workers for particular inherited genetic traits or environmentally induced changes in the genetic material of certain cells on the assumption that the traits or changes may predispose them to illness. It has been used by some manufacturing companies and utilities for medical evaluation and by others for research.

There are two inherently different kinds of testing, genetic monitoring and genetic screening, whose results can be used in the workplace for different purposes.

Genetic monitoring involves periodically examining a group of workers by collecting blood or other body fluids to assess whether genetic damage has occurred in certain cells. This damage may indicate exposure to a hazardous agent, such as a carcinogenic chemical or ionizing radiation. It may also indicate the possibility that the exposed group will be at an increased risk of developing disease, most likely cancer. The procedure focuses on the risk for the exposed group as a whole because there is no evidence to suggest that it could be used to identify which individuals in the group are at increased risk. If the scientific validity of genetic monitoring were fully established, it would have potential as an early warning system, by indicating that exposures to known or suspected carcinogens are too high or that a previously unsuspected chemical should be viewed as a potential carcinogen.

In contrast, genetic screening, when used in the workplace, is a one-time testing procedure to determine if a person has particular genetic traits, regardless of whether the person has been exposed to a hazardous substance. The traits are identified through laboratory tests on body fluids, usually blood. Some scientists have hypothesized that these genetic traits might predispose an individual to adverse health effects in the presence of particular chemicals. While normally not harmful, the traits theoretically may make the individual more susceptible to blood-damaging chemicals, pulmonary irritants, oxygen deprivation, or other physical or chemical stresses in the workplace.

In sum, genetic screening has the potential to determine individual susceptibility to certain hazardous agents. It may be that, in time, genetic monitoring also will be able to determine individual susceptibility; however, currently it appears only to have potential for assessing a chemical's effect on an exposed population as a whole. Because of this distinction, screening could be used to exclude genetically susceptible individuals from jobs where they would be exposed to hazardous substances, whereas monitoring would most likely indicate a need to lower exposure levels for a group exposed to a previously unknown hazard.

POTENTIAL BENEFITS AND RISKS

Although genetic testing is still in its infancy, its advocates believe that it might be able to play an important role in the prevention of occupational disease. It is technologically and economically impossible to attain a no-risk workplace by lowering the level of exposure to hazardous substances to zero. However, if individuals or groups who were predisposed to occupational illness because of past exposure to hazardous substances or particular genetic makeup could be identified, preventive measures could be taken by the company or the workers themselves. In addition to the obvious and significant benefits from preventing serious illnesses, there could be indirect benefits, such as a reduction in the costs associated with occupational illness for employers, employees, and society. These costs include medical, insurance, and legal expenses; time lost from work; and disability or unemployment payments.

The use of this technology, however, raises several questions. Can the techniques truly predict an association between genetic makeup or genetic damage and disease? How much of the variation in risk can be attributed to such predisposing genetic factors and how much to variation in environmental exposure? Since many of the genetic traits sought in screening happen to be distributed unevenly among some races and ethnic groups, could the use of the tests result in discrimination on the basis of race or national origin? How will the availability of the tests affect the employer's responsibility for maintaining a safe workplace? How might these procedures affect efforts to reduce the level of hazardous substances in the workplace? If the tests are predictive, to what degree should society protect high-risk individuals or groups, at what cost, and who should bear that cost?

Findings

Because genetic testing is an emerging technology, there is insufficient evidence to assess many of its potential benefits, risks, and impacts. However, this report does examine the degree to which it has been used, the current stage of its development, expected future developments, and various legal, ethical, economic, and policy issues that it raises. This examination provides the basis for a discussion of the broader social issues and the options for possible congressional action.

Survey of the use of genetic testing

There have been conflicting accounts about the extent of testing and the use of the results. None of the accounts examined by OTA was based on a rigorous, scientifically valid survey. Therefore, in order to reduce the confusion and speculation and to provide necessary data for policy analysis, OTA surveyed major U.S. industrial companies, utilities, and unions about their use of this technology.

The survey was conducted for OTA from February 25 to June 8, 1982, by the National Opinion Research Center (NORC), a nonprofit survey research corporation affiliated with the University of Chicago. NORC sent confidential questionnaires to the chief executive officers of the 500 largest industrial companies and 50 largest private utilities in the United States and to the presidents of 11 major unions representing the largest number of employees in these companies. Of the 366 (65.2 percent) organizations responding, 6 (1.6 percent) were currently using one or more tests, 17 (4.6 percent) used some of the tests in the past 12 years, 4 (1.1 percent) anticipated using the tests in the next 5 years, and 55 (15 percent) stated they would possibly use the tests in the next 5 years. Of the 17 organizations that have tested in the past 12 years, 5 are currently testing. None of the four responding unions reported any testing.

For each type of test, companies were asked about the circumstances under which the tests were done (that is, routinely, for research, or for other reasons) and how employees were selected. Respondents generally tested routinely or for other unspecified reasons. Testing for sickle cell trait was most often based on ethnicity; for other types of tests, employees were selected on the basis of job category. No organization reported basing a genetic test on an employee's sex.

The 18 respondents who are testing or have tested took various actions based on the results. The most common action reported—by eight organizations—was informing an employee of a potential problem. Five organizations transferred employees. Two companies suggested the employee seek another job, and one changed or discontinued a product.

In evaluating the results of the survey, several caveats must be considered. The most important of these are:

- Since the questionnaire instructed respondents to include any instances of testing, positive responses can include isolated cases as well as long-term testing programs.
- The questionnaire was not structured to provide information on the numbers of workers tested.
- Results of this study are more representative of the larger companies in this survey than other groups, since more large companies responded than did small ones.
- Since approximately one-third of the population did not respond and the number of organizations testing is very small, any generalizing of these results to the study population as a whole is not warranted.

The state of the art

This assessment took a two-stage approach to analyzing the scientific data available on genetic testing. First, the laboratory tests themselves were evaluated to determine their reliability and validity. Then the available studies were evaluated to determine if there is a correlation between the genetic damage or trait in question and an increased risk for disease. **None of the genetic tests evaluated by OTA meets established scientific criteria for routine use in an occupational setting. However, there is**

enough suggestive evidence to merit further research.

GENETIC MONITORING

The concept of monitoring workplace populations for genetic damage from chemicals or ionizing radiation is well grounded on a theoretical and experimental base. Ionizing radiation and a wide range of chemicals cause damage to the genetic material in experimental animals and, in some cases, humans. This damage may result in mutations, which are changes in the genetic information. The consequences of increasing the mutation rate of a population are not well understood, but mutations have been implicated in several diseases, most notably cancer.

There are two major types of genetic monitoring methods—the established cytogenetic methods which detect major structural changes in chromosomes and the newer noncytogenetic methods, which detect damage to the DNA (deoxyribonucleic acid). The noncytogenetic methods, for the most part, are still in experimental stages, but eventually could lead to faster and less expensive monitoring methods.

The detection of chromosome damage using cytogenetic techniques is a fairly complex procedure. It requires skilled laboratory technicians and is often labor intensive. But if laboratory variables are kept constant, chromosome damage can be determined reliably.

There are two stages involved in the assessment of genetic monitoring. The first determines whether the agent actually causes the genetic damage in a manner such that increasing dosages of the agent gives increasing amounts of damage (dose-response). The second stage of the analysis asks whether the observed genetic damage actually will predict an increased risk for disease. If good scientific evidence is available to support both stages of the analysis (this is, that the hazardous agent causes genetic damage, and that this damage predicts an increased risk for disease), then the assumption can be made that the agent causes disease. OTA found that there are some studies where a dose-response relationship has been established, but there are few studies showing a correlation between genetic damage and an increased risk for disease.

A large number of studies on workplace populations, using cytogenetic techniques, have been done, but there are several factors which make the interpretation of these studies difficult. In very few cases has the level of exposure of the workers to the hazard been documented, making the establishment of a dose-response relationship impossible. Also, it is fairly well established that other factors such as age, smoking and drinking habits, nutritional status, and the presence of disease can cause differences in the level of chromosomal damage. Because most studies have not taken these factors into account, there is a large variability in both exposed and unexposed populations. When exposed populations are studied, rarely is there found more than a twofold increase in damage over the average of the unexposed population. Thus, given the variability of the unexposed population, interpretations of these studies are difficult. Finally, it is not known whether chromosomal changes in blood cells reflect the presence of chromosomal damage in internal organs.

Studies done on populations exposed to ionizing radiation, including atomic bomb survivors in Japan, are less equivocal than those for chemical exposure, mainly because radiation exposure levels are more easily documented. The evidence does show an increase in chromosomal damage with increasing dose of radiation. This damage, though, has not been correlated with an increased risk for disease with one exception. Extensive studies on the bomb survivors have shown clear dose-related increases in both chromosomal abnormalities and various cancers for these populations as a whole. Yet there seems to be no correlation between the frequency of chromosomal abnormalities for a given individual and his or her risk for cancer.

Currently, genetic monitoring has the potential for use as a biological indicator of exposure to workplace chemicals or ionizing radiation and could aid in the identification of hazardous agents. The correlation of induced genetic damage with risk for disease has been shown statistically only for the Japanese population exposed to ionizing radiation from the atomic bombs. For people exposed to hazards in the workplace, more information is needed to elucidate other environmental and genetic factors which may contribute to increased risk for disease.

GENETIC SCREENING

Differential susceptibility to chemicals has been predicted, in part, from differential reactions to drugs, which have been extensively documented. Explicitly defining this genetic differential susceptibility is not yet possible given the current state of knowledge; however, some data do exist on a few genetic traits, implicating them in susceptibility differences to certain chemicals. The list probably represents only a small percentage of the genetic traits involved in responses to chemicals. This report examines the following traits: glucose-6-phosphate dehydrogenase (G-6P-D) deficiency, sickle cell trait, alpha and beta thalassemia trait, NADH dehydrogenase deficiency, serum alpha$_1$-antitrypsin (SAT) deficiency, aryl hydrocarbon hydroxylase (AHH) inducibility, slow v. fast acetylation, human leukocyte antigens (HLA), carbon oxidation, diseases of DNA repair, and several other less well-characterized genetic traits.

OTA found that most tests for identifying these traits are accurate and reliable, but only when applied to subgroups already suspected of having the trait at a relatively high prevalence. Because the predictive value of these tests is low when used in the general population, studies using these tests could be seriously flawed. In fact, the predictive value of the test, which is based not only on accuracy but also on the prevalence of the trait in the population, will only be high when the prevalence of the trait is high.

There is some suggestive evidence, from adverse drug reactions and illnesses resulting from exposures to chemicals, that associations may exist between certain traits and risk for disease from particular occupational exposures. This report reviewed occupational studies on several genetic traits and found that the data were not extensive enough to draw any conclusions on the correlation between given genetic traits and risk for disease. On the other hand, the data are suggestive of these correlations, and research seems indicated for attempting to determine these relationships.

Genetic testing and the law

Genetic testing raises legal questions related to workplace safety and employee rights. Although the law generally has not dealt with genetic testing, many existing legal principles are directly applicable to the issues raised by this technology. Moreover, employers and unions could negotiate mutually agreeable solutions to the problems raised by genetic testing. Unions, however, have no legal duty to bargain over such issues or to take special steps to protect workers who might be at increased risk.

The employer has the legal responsibility for workplace safety. Failure to meet the responsibility can result in costly judgments or civil or criminal penalties against the employer. This responsibility would not require the employer to use genetic testing, even if it were highly predictive of future illness. If the employer chose to use a highly predictive test, it would probably be negligent if it ignored the results and placed employees in a high-risk rather a than low-risk environment. However, recovery of damages by such an employee who developed the predicted illness would probably be barred by the "exclusive remedy" provision of workers' compensation laws and possibly by the doctrine of assumption of the risk, if the employee had been informed of the risk. If the risk had been concealed from the employee, recovery probably would not be barred under workers' compensation laws, and the employer would face the possibility of punitive damages.

Under the Occupational Safety and Health Act of 1970 (OSH Act), the Secretary of Labor is empowered to promulgate standards that protect all employees from toxic substances to the extent that the standards are directed toward a significant risk to health and to the extent that they are technologically and economically feasible. These standards can, among other things, set maximum exposure levels, require personal protection gear, and require various medical procedures. The feasibility requirement may leave some percentage of exposed workers at risk, depending on the circumstances of the particular hazardous substance and industry. Of those workers at risk, some may be genetically susceptible and others may be at increased risk because of genetic damage. An open question is whether the courts would allow a standard designed to protect a very small number of susceptible individuals or would invalidate it on the grounds that it failed to address a significant risk because of the small number of workers involved.

The OSH Act and regulations thereunder neither prohibit nor require genetic testing. However, the Secretary of Labor has broad authority to regulate employer medical procedures as long as the regulation is related to worker health and meets the feasibility and significant risk requirements. Therefore, the Secretary could require genetic testing in its various forms, if the techniques were shown to be reliable and reasonably predictive of future illness. The Secretary also could regulate the use of genetic testing, but only to the extent that the regulation was related to employee health. The act grants no authority over rights or conditions of employment per se and no authority to protect applicants for employment from discrimination.

State and Federal laws place few restrictions on how medical exams or testing procedures may be conducted in the workplace and what the employer does with the resulting information other than the requirements that the procedure not be negligently performed and that the employee be informed of potentially serious health risks. Submission to medical exams, which include various tests, can be a valid condition of employment. As a result, employees or applicants would have no right to refuse to participate without jeopardizing their job. Moreover, participation in research can be a valid condition of employment. How much the employee needs to be told about the research is unclear, except in two cases. If the research were federally funded, subjects must understand the risks and other aspects of the study and consent to them. A few States require research to be reviewed by special boards in order to protect the interests of human subjects, and these boards may require informed consent.

With respect to the data generated by genetic testing, there are few requirements regarding confidentiality except in the State of California. But employees have a right of access to medical records under Occupational Safety and Health Administration (OSHA) regulations and unions have a similar right under a recent decision by the National Labor Relations Board. This access could help prevent abuse of genetic testing. However, those who face the greatest risk of being denied employment because of their genetic makeup—job applicants—would not have access to the test results.

For those applicants or employees who were subject to some adverse job action because of their genetic makeup, Federal and State antidiscrimination statutes may offer some relief. However, they do not deal specifically with genetic screening except for a few State statutes that prohibit employment discrimination on the basis of certain genetic traits, usually sickle cell trait.

Title VII of the Civil Rights Act of 1964 prohibits discrimination in employment based on race, color, religion, sex, or national origin. In addition to intentionally discriminatory actions, neutral employment practices that have a disparate impact on a protected group may violate title VII. Some types of genetic screening, such as for sickle cell trait, would have a disparate impact; therefore, an adversely affected genetically susceptible employee in one of those classes would have a prima facie case of discrimination. Then, the employer would have the burden of justifying the screening program by demonstrating its relation to legitimate job requirements or business needs. It is presently unclear whether using genetic testing to screen out employees who might beome ill in order to avoid the cost of engineering controls is a business necessity. Nor is it clear whether the employee's capacity to perform the job without a risk of future illness is a legitimate job requirement. However, it is clear that any job selection method must be predictive of the characteristic for which it allegedly selects. Since the ability of genetic screening to identify workers at increased risk for disease has not been demonstrated, a program that had a disparate impact on the employment opportunities of the classes protected by title VII probably would violate that act.

The Rehabilitation Act of 1973 prohibits employment discrimination against otherwise qualified handicapped people by employers who are

Government contractors or recipients of Federal assistance. Virtually all of the States have similar statutes, and the State laws usually offer broader protection to handicapped people. These statutes offer a greater potential than title VII for aiding the employment opportunities of genetically susceptible individuals; however, for those laws to be applicable, two currently unresolved legal questions must be settled in favor of the employees. The first is whether or not a particular genetic makeup is a handicap. If not, these employees would have no rights under these laws. If it is a handicap, the next question is whether employment may be denied to handicapped individuals on the basis of a reasonable probability of future illness. If the courts were to rule that future risk of illness was not a legitimate area of inquiry for employers, the Rehabilitation Act and similar statutes would prohibit adverse job actions on the basis of genetic makeup. If risk of illness were recognized as a legitimate concern, the employer would have the burden of showing the genetic screening techniques were reasonably predictive of illness. Even if the employer demonstrated this, however, it might have to accommodate the "genetically handicapped" employee anyway. But such accommodation probably would not require the installation of expensive engineering controls to lower exposure.*

Ethics of genetic testing

Because genetic testing is relatively new and has not been widely used, there is little direct experience on which to make judgments regarding its use. Nor are there direct legal precedents. Under these circumstances, it is appropriate for policymakers and others involved in decisions concerning this technology to look to ethical principles for guidance.

Ethics may be defined as the study of moral principles governing human action. These principles, or general prescriptive judgments, create moral duties that guide action in particular circumstances. Sometimes, however, the principles conflict in their application and provide no clear guidance. Then, difficult choices must be made. Such is the case with genetic testing in the workplace.

Genetic screening and monitoring are not inherently unethical. The tests are morally justified to the extent they enhance worker health in a manner consistent with established ethical principles. Whether or not they are consistent with these principles will depend on how the tests are done and how the information is used.

Ethical principles regarding the duties of company medical personnel toward workers are often conflicting or not well established. Therefore, they offer little specific guidance about the manner in which tests should be conducted with the exception of procedures done for purposes of medical research. In cases of research on humans, ethical principles are well established and provide for the rigorous protection of individual rights and interests.

Ethical principles constrain how the results of genetic testing may be used. In the absence of a significant correlation between genetic endpoints (traits or evidence of damage from exposure) and disease, it would be unethical for the employer to act adversely to the employee's interests, such as by denying him or her a job.

In the hypothetical case of a strong correlation between genetic endpoints and disease, the morally correct course of action is significantly less clear. For screening, the employer might justify excluding susceptible workers from certain jobs on the grounds of benefiting the employees. On the other hand, employees might claim that they have the right to decide whether to assume the risk. Whether or not genetically susceptible people are entitled to protection from discrimination or compensation for harm depends on which of several theories of justice is chosen. For monitoring, the most ethically feasible course of action for an employer would be to inform the workers of adverse findings and to reduce worker exposure. Failure to do so would be inflicting harm, and it is unlikely that the group would consent to assuming this risk.

Economic evaluation of genetic testing

Genetic testing in the workplace has potential benefits and costs to workers, employers, and society as a whole. The magnitude and distribution among the sectors of society of these benefits and costs will help determine the desirability of this approach to improving occupational health. Two techniques of economic evaluation—cost-benefit and cost-effectiveness analysis—are methods for collecting, organizing, and presenting evidence about the benefits and costs of alternative courses of action so that choices can be better informed. They are systematic approaches to examining the tradeoffs among the different kinds of consequences—for example, dollar outlays today v. improved levels of health 5 years hence—stemming from a decision.

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*OTA is conducting a study on the use of engineering controls to enhance worker safety and health.

The usefulness of economic evaluation rests on its ability to improve decisions. Even when economic analysis is severely limited by uncertainties about the magnitude, direction, or value of certain consequences, as with genetic testing, it can still be a useful exercise. The identification of key areas of uncertainty, for example, can be used to set priorities for further research. Thus, economic evaluation can be used to dissect and examine alternative strategies in order to understand their underlying assumptions and uncertainties.

In the case of genetic testing, rigorous economic analysis of the costs and benefits is not possible because of the lack of knowledge about the association between test results and risk of disease, the numbers of people to whom testing could be applied, and the amount of occupational disease that could be prevented. If additional information became available, economic analysis could provide a rough sense of the benefits, burdens, and tradeoffs associated with genetic testing programs.

Congressional issues and policy options

ISSUE: What actions could Congress take with respect to genetic testing in the workplace?

OPTIONS:

A. Maintain the status quo.

Congress could choose not to take any action to stimulate, constrain, or regulate genetic testing. This would allow private parties to continue research into the merits of the technology. Constraints on its use would develop through court rulings in lawsuits between these parties or by negotiations between companies and unions. Interested congressional committees could continue their practice of holding oversight hearings to raise the issues for public discussion.

The primary argument supporting this option would be the view that congressional action would be premature. The technology is not being widely used, and it is primarily in the research phase of its development. In addition, there are existing constraints on its potential misuse. These include the possibility of lawsuits and adverse publicity. Finally, much of the important information necessary for legislation is unavailable because it is unknown. For genetic screening techniques, this information includes the number of workers who might be genetically predisposed to disease, the extent to which they might face adverse employment actions, the availability of other employment opportunities, and the cost of safeguarding these workers. For genetic monitoring techniques, this information includes their predictive value, the extent to which they might be used, and the costs associated with either using or not using them.

The arguments against this option relate to how society controls an emerging technology. Many policy decisions will need to be made with respect to genetic testing, and arguably Congress is a better forum for doing so than the courts or private parties. Congress can gather all information and viewpoints and then balance the conflicting interests. In addition, while the courts often play a major regulatory role for any technology, they are limited in their ability to encourage the development of a technology in a positive manner. However, Congress can do so by providing funds for research or other incentives.

B. Stimulate the technology's development and use.

Congress could stimulate the technology by providing money for research on the techniques, for epidemiological studies to determine associations between genetic endpoints and disease, and for basic research on the cause of occupational disease in general. If genetic testing could be developed to the point where the tests are predictive of an individual's or group's increased risk of occupational illness, their use could result in a number of direct and indirect benefits. The principal direct benefit would be a lower incidence of occupational disease among workers. They and their families would be spared some of the pain, cost, and emotional trauma that accompany illness. In addition, employers would save some of their direct and indirect costs of occupational disease—employee time lost from work, insurance premiums, legal fees, and monetary damages assessed in lawsuits. Society would benefit through the greater health and productivity of its work force. A major indirect benefit of developing this technology might be a greater understanding of the causes of occupational disease and disease in general.

The principal argument against this option is the concern about the potential misuse of the technology and about potential adverse impacts. Some of these concerns relate to unfair employment discrimination and attention being directed away from other ways to address occupational diseases. These concerns might be dispelled by regulation to direct the technology's development in socially desirable ways. In fact, if the tests were highly predictive of future illness, OSHA could require their use and constrain how they were used, so long as those constraints were shown to enhance worker health and were not directed merely toward prohibiting unfair employment practices.

Another drawback to this option is the fact that there is no definitive information on the amount of occupational disease that could be prevented by genetic testing, even if the tests were reliable predictors of disease. Similarly, there is no information on what it would cost to develop the tests to the point of clinical usefulness.

C. Prohibit the use of genetic testing in the workplace.

The principal reason for prohibiting genetic testing in the workplace would be concern over its potential misuse, particularly at its current stage of development where its ability to predict future disease has not been demonstrated. This potential for misuse probably would be greater for genetic screening than genetic monitoring because the former is targeted toward identifying individuals at increased risk while the latter focuses on groups at increased risk. However, concern exists that employers might use either type of test to exclude individuals from jobs. Existing law may offer protection in some circumstances, but there are many questions to be resolved. The collective bargaining process could be used by unions to negotiate protection for workers, but the primary focus of bargaining has been economic matters. While health matters have also been important, little, if any, negotiating has occurred with respect to genetic screening. In addition, most of the work force is not unionized. Moreover, these remedies are not helpful if a susceptible person does not know why he or she was denied a job. Finally, while ethical principles provide guidance for the proper use of this technology, it is difficult to know if they are being followed.

The principal drawback to this option is that it is a drastic solution to the problem of potential misuse. Genetic testing does not appear to be widely used. Law, ethics, and public opinion provide incentives against its misuse. Moreover, banning its use would prevent research that might determine its usefulness in preventing occupational disease or provide basic knowledge about occupational disease.

Another argument in favor of this option would be the claim that an employee's risk of future illness is not an appropriate factor for job selection, even if screening or monitoring were highly predictive. Employees have no control over their genetic makeup and generally have no control over previous exposures to harmful agents. In addition, their increased risk would not affect their current ability to do the job.

There are at least two counterarguments to the assertion that risk of illness should not be a job selection factor. First, society accepts the proposition that immutable characteristics can be proper criteria for employment selection. Intelligence is at least an implicit selection criterion for many professional jobs and physical attributes are exceedingly important for jobs ranging from professional basketball to neurosurgery. Second, this viewpoint places the autonomy interests of the individual above the interests of society in lowering the costs of occupational illness even when it may not be feasible to take other steps, such as lowering exposure.

D. Regulate the technology.

This option represents a judgment that any risks presented by the technology can be controlled and that the claimed benefits will be of value to society. The option would permit research to continue, yet constrain the manner in which genetic testing is used. One type of constraint would be limitations on what job actions employers could take on the basis of test results. Another type of constraint would be a requirement that the tests meet minimum standards of scientific validity before employment decisions were made on the basis of the results. Such a statute need not specify detailed standards; it could adopt a standard such as "reasonably predictive of future illness" and allow the appropriate agency to provide details.

This option has the advantage of addressing the potential risks of genetic testing immediately and in a comprehensive manner rather than waiting for the law to develop on a case-by-case basis through the courts. Congress may be uniquely able to study the problem fully, balance competing interests, and provide comprehensive yet targeted solutions.

A possible drawback of this option is that the problem may not yet be "ripe" for congressional action. On the basis of available evidence, genetic testing in the workplace does not appear to be widespread. Moreover, there is no available evidence about: 1) the number of workers who potentially could be screened or monitored if the tests were sufficiently predictive, 2) the number who might be excluded from jobs, 3) the ease with which excluded workers could find comparable jobs, and 4) the costs of various regulatory alternatives.

E. Encourage the development of voluntary guidelines on the acceptable use of genetic testing.

Congress could request the National Academy of Sciences or a similar body to establish a special commission of representatives from industry, labor, academia, and other sectors of society to draft voluntary guidelines for the use of the tests. This would allow the parties most involved to make the difficult value judgments in balancing competing interests and would avoid direct governmental regulation.

ISSUE: How could Congress regulate genetic testing in the workplace?

OPTIONS:

A. Constrain employment actions that may be taken on the basis of genetic testing.

Congress could address many of the concerns raised by genetic testing by regulating how employers may use the results of the tests, even if they were highly predictive. The following represent some possible elements of such an approach: 1) prohibit job exclusion on the basis of genetic makeup or genetic damage, 2) prohibit job transfers because of genetic makeup or genetic damage unless the transfer were to a comparable job at comparable pay and benefits, 3) require strict confidentiality of medical information, and 4) require that employees be told the results of testing and be given counseling.

This option clearly would protect the interests of workers, preventing potentially serious consequences to individuals who have no control over the reason for the discrimination. In addition, no difficult judgment would have to be made as to how predictive the tests should be before they are permitted.

There are at least two major disadvantages to this option. First, it may be too broad. If not carefully drafted, a statute could reach genetic diseases (not traits) that do affect an employee's current ability to perform the job safely and effectively. It is generally accepted that inability to perform a job, even for medical reasons, is a valid criterion for job selection. Second, if workers with certain traits were in fact predisposed to occupational illnesses and chose to ignore that information, the additional direct and indirect costs of their illnesses eventually would be borne by society. This would be the case even if employers were required to install additional engineering controls, since the costs of those controls would be passed on to society. On the other hand, if excluded workers were unable to find comparable jobs, society would bear the costs of lost productivity and possibly additional unemployment payments. The answer to the question of who should bear the costs associated with genetically predisposed or damaged individuals will depend not only on economic analyses but on prevailing political views of distributive justice.

B. Prohibit employment decisions on the basis of genetic testing unless the employer can demonstrate that the results are reasonably (or substantially) predictive of future illnesses.

This option places the burden on an employer to justify the claimed correlation between test results and risk of illness. The specific criteria for meeting a necessarily general statutory standard could be provided by agency regulation and case law.

There are several advantages to this option, especially when compared to option A. First, it focuses on the immediate concern of job denial on the basis of poorly predictive tests, thus protecting employees' interests. Second, it protects employers' interests in lowering their costs from occupational diseases by allowing the exclusion of certain workers when there is a rational, scientific basis for doing so. Third, it would allow research on the techniques to continue.

The principal drawback of this option is that it could be a de facto determination without a full public debate that future risk of illness is a proper job selection criterion. On the other hand, there is a substantial lack of the type of information desirable for deciding this fundamental issue at this time.

C. Amend the Rehabilitation Act of 1973 to state that genetic makeup is a handicap and clarify whether individuals who are genetically predisposed to illness are considered to be "otherwise qualified" within the meaning of that act.

A major advantage of this option would be working with an existing statute rather than devising an entirely new one. Sections 503 and 504 of the Rehabilitation Act deal with problems that conceptually are very similar to those posed by genetic screening. If applied to genetic screening, the act would require at a minimum that the tests be reasonably predictive of future illness.

On the other hand, this option would force legislative activity into an existing statutory framework that may not be completely suited to genetic screening. The Rehabilitation Act was designed to bring millions of handicapped people into the mainstream of American life. Genetic screening has not created a problem anywhere near the magnitude of that addressed by the Rehabilitation Act. Moreover, section 503 requires employers to take affirmative action to employ the handicapped. Congress may not wish to require affirmative action to employ people who are genetically predisposed to occupational illness, if that predisposition can, in fact, be demonstrated.

D. Require that research on employees be done according to existing Federal regulations designed to protect human subjects of research.

The Department of Health and Human Services has promulgated regulations governing federally funded biomedical and behavioral research on humans. The regulations contain a number of provisions designed to protect the interests of the research subjects. Requiring private companies to follow these regulations in research involving genetic testing or any other kind of research done in the workplace would mitigate the potential for abuse.

E. Require full disclosure to employees and their representatives of the nature and purpose of all medical procedures performed on employees.

Under current law, employees and unions have access to employee medical records, but employers are not required to disclose the nature and purpose of medical procedures and how the results are used. Required disclosure of this information to the employee at the time the procedure was being performed would be a strong incentive to employers for self-regulation. If workers and their medical advisors had full knowledge of a company's medical procedures, they could take steps to prevent abuses, through negotiation or legal action. Publicity alone could prevent the worst abuses. This would also protect the autonomy interests of workers by allowing them to be part of a decisionmaking process that affects their health and economic interests. Some of the arguments against this option would be that it might be burdensome and costly for employers and that it would intrude too much on the professional judgment of the occupational medical specialist.

ISSUE: How could Congress foster the development and use of this technology?

OPTIONS:

A. Fund research for the development of tests with high reliability and validity.

Genetic variability and differential susceptibility to toxic chemicals are well-established concepts in the scientific literature. Currently there are many genetic screening tests which could be done in a workplace setting to detect potentially susceptible individuals. For the most part, these tests are accurate, reliable, and valid for identifying the genetic traits in question when applied to subgroups already suspected of having the trait at a relatively high prevalence; a notable exception is the test for aryl hydrocarbon hydroxylase (AHH) inducibility. Research on developing tests for those traits which are more prevalent in the population should receive higher priority because they are more likely to have a high predictive value. The only test covered in this report which falls into this category is AHH inducibility.

With respect to genetic monitoring, the notion that exposure to toxic chemicals and ionizing radiation can cause genetic damage in humans is less well established scientifically than the concept of differential susceptibility. However, there is an overwhelming amount of evidence that this is true in experimental mammals. Moreover, the impact of genetic damage on one's risk for disease, especially cancer, or on future generations is not known, yet the current thinking of the scientific community is that increased amounts of genetic damage is generally deleterious.

Alternatives are needed to the time-consuming cytogenetic tests currently in use. If genetic monitoring is to be done on a large scale, the availability of automated tests becomes important. The development of various noncytogenetic methods could be useful in this respect. Those that show promise currently include tests for detection of: mutagens in urine, alkylated hemoglobin, HGPRT mutation in lymphocytes, hemoglobin mutations, chemically damaged DNA bases, and LDH-X variants in sperm. For both cytogenetic and noncytogenetic tests, a better understanding of the factors that contribute to genetic damage in the absence of occupational exposure is needed (that is, a "normal" or baseline response) in order for the tests on exposed populations to be meaningful.

The government agencies which could be involved in these studies include the Environmental Protection Agency (EPA), the National Institute for Occupational Safety and Health (NIOSH), and the National Institute for Environmental Health and Safety (NIEHS).

B. Fund epidemiologic studies in occupational settings directed by NIOSH or NIEHS.

Data are most lacking concerning the correlation of genetic traits or genetic damage to an increased risk for disease. Epidemiologic studies in an occupational setting can address this problem. If these studies were to be undertaken, they must use good epidemiological practices and document exposures. Studies should only be undertaken if they are likely to yield statistically reliable data. For instance, genetic monitoring studies would require exposure levels high enough to yield a clear-cut statistical response between exposed and nonexposed groups without having to use excessively large numbers of people. Especially important would be to establish a dose-response relationship. Genetic screening studies would have to focus on genetic traits which have a significant prevalence in the population (greater than 1 percent).

Epidemiologic studies are very costly and difficult to control, especially if they run over long time periods. Some genetic screening studies could be done in a short time (1 to 3 years) once a population with the trait was selected because, presumably, the symptoms of disease resulting from exposure would manifest themselves soon after exposure. These traits include the red blood cell traits. Most of the other traits reviewed here are potentially correlated with diseases which have a long latent period, such as emphysema and cancer. To correctly assess the exposure information with the disease endpoint, much longer epidemiologic studies (10 to 30 years) are necessary.

For genetic screening, higher priority should be given to studies on traits which have a high prevalence in the population. These include SAT deficiency, AHH inducibility, carbon oxidation ability, and the association of particular human leukocyte antigens with risk for disease.

Epidemiologic studies using genetic monitoring techniques would have to be long term in order to determine the association between genetic damage and cancer. The chemicals chosen for study would have to be selected carefully. Many of the agents discussed in this report are known already to cause cancer in humans (for example, ionizing radiation, benzene, vinyl chloride), and occupational exposure to these is very low and possibly not detectable by the genetic techniques now in use.

C. Establish a federally funded data bank, directed by NIOHS, EPA, or NIEHS, to be used in the study of the causes of differential susceptibility to occupational disease.

Because the study of the effects of harmful agents includes many scientific disciplines, it would be useful to have the relevant data collected in an accessible location. This computerized data bank could include not only genetic factors affecting toxicity, but developmental, aging, nutritional, and lifestyle factors as well. The data bank would include epidemiologic studies that have been or are being done in occupational settings, either governmentally or privately funded (somewhat in the same manner as EPA's Gene-Tox Program). Those working in the field of genetic toxicology could draw on the information in the bank in order to design studies and to prevent duplication of effort. The toxicology data would be of considerable value to various regulatory agencies in their standard setting.

Chapter 2

Introduction: Occupational Illness and Genetic Testing

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Chapter 2

Introduction: Occupational Illness and Genetic Testing

The problem of occupational illness

Occupational illness is a major problem in this country. In a 1981 private sector work force of approximately 75.6 million people, there were an estimated 126,000 cases of work-related acute illness, which resulted in more than 850,000 lost workdays, according to the Bureau of Labor Statistics (2).* Moreover, an estimated 5 percent of all cancers are believed to be associated with exposure to harmful substances in the workplace (17).** Litigation over illness claimed to have resulted from one substance alone—asbestos—could result in insurance payments as high as $38 billion over the next 35 years, and one major manufacturer of asbestos, faced with more than 16,500 lawsuits, has filed for reorganization under the Bankruptcy Act (21,22).

The health risks posed by the workplace environment vary with the industry and the type of job but are often associated with exposures to harmful substances or agents. These substances or agents include minerals, chemicals, and ionizing radiation. This report focuses on an emerging technology, genetic testing, that may be useful in reducing occupational illness arising from such exposure, especially to chemicals and ionizing radiation.

Genetic testing, as used in the workplace, encompasses two types of techniques. Genetic screening involves examining individuals for certain inherited genetic traits (9). Genetic monitoring involves examining individuals periodically for environmentally induced changes in their genetic material. The assumption underlying both types of procedures is that the traits or changes may predispose individuals to illness. Although this technology is still in its infancy, genetic testing potentially could play an important role in the prevention of occupational diseases. It is technologically and economically impossible to attain a no-risk workplace by lowering the level of exposure to hazardous substances to zero. However, if individuals or groups predisposed to occupational diseases could be identified, other preventive measures could be specifically directed at those persons. This is the promise of genetic testing. At the same time, however, the technology has potential drawbacks and problems. For example, it could result in workers being unfairly excluded from jobs or in attention being directed away from efforts to "clean up" the workplace.

Because genetic testing is still in its infancy, many of its potential impacts—both positive and negative—at present cannot be precisely defined. Nonetheless, it is not too soon for society to begin to consider how genetic testing may affect us. In industry, genetic testing has been little used to date, but an Office of Technology Assessment (OTA) survey has found several companies interested in using it in the future. Thus, this report, requested by the Committee on Science and Technology of the U.S. House of Representatives as an assessment of genetic testing, can provide a foundation for future debate as this technology continues to develop.

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*The accuracy of these figures is subject to much debate among the experts. The Bureau of Labor Statistics itself acknowledges that the figures understate the amount of occupational illness because they do not adequately reflect chronic diseases and diseases with long latency periods because of problems with detection and recognition (2). They are used here simply to provide the reader with a general notion of the magnitude of the problem.

**Estimating the amount of cancer associated with occupational exposures is extremely difficult, and experts often disagree. In the past, estimates have ranged from 5 to 38 percent. In 1981, OTA suggested that almost all estimates of work-related cancer fit into a range of 10 (± 5) percent of all cancer (14). Data presented at an international conference on quantification of occupational cancer suggest that the OTA estimate may have been too high (17). Five percent now appears to be the figure acceptable to most experts, although some experts still argue for estimates greater than 20 percent (17,19).

Health hazards in the workplace

Of the many different kinds of hazardous substances or physical agents in the workplace, chemicals and ionizing radiation are the two categories of hazards for which genetic testing has been used and for which some data exist for evaluating the scientific validity of that testing.

Hazardous chemicals

Many, but not all, chemicals are hazardous. Chemicals may be irritating, toxic, mutagenic, teratogenic, and/or carcinogenic. They may enter the body through the skin, the lungs, and the gastrointestinal tract. Contact with skin can produce irritation and dermatitis. Breathing chemicals can cause irritation or damage to the upper respiratory tract and the lungs. Contact with some chemicals through virtually any route may cause cancer.* Exposure to more than one chemical may result in a synergistic effect—damage greater than the combined damage of the individual exposures. The degree of risk posed by a hazardous substance depends on the degree to which a person is exposed to it, and risks can be reduced by reducing exposures.

There are more than 55,000 different chemicals in commerce (14). The percentage of these that are hazardous at current exposure levels is unknown. Chemicals are found not only in companies that produce them but throughout the manufacturing sector. The National Occupational Hazard Survey (NOHS), conducted by the National Institute of Occupational Safety and Health, estimated that approximately 8.5 million workers were exposed to chemical hazards in the manufacturing sector during the years 1972 to 1974 (11). Because the manufacturing labor force grew at a 0.7 percent annual rate during the years 1973 to 1979, the number of exposed workers in manufacturing in 1980 may have totaled 8.9 million (11). According to the Occupational Safety and Health Administration, exposure to chemicals is the most important occupational health problem because of the number of workers involved (13).

Photo credit: Occupational Safety and Health Administration

Exposure to chemicals in work-related environments over long periods of time can be hazardous to health

For the individual, the hazard of working with chemicals is compounded by the likelihood of multiple exposures. A worker may be exposed to numerous chemicals at any one time or over a long period of employment. Rubber workers, for example, are exposed to an estimated 3,000 chemicals (18). The NOHS data indicate that more than 280 million chemical exposures* occurred in the manufacturing sector during 1972 to 1974 (18). By 1980, based on growth projections in the number of workers and in the number of chemicals,** chemical exposures among workers in manufacturing were estimated to be 361 million.***

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*The National Institute of Occupational Safety and Health has published a list of approximately 2,400 suspected carcinogens (14).

*NOHS defined "exposure" as "employees' actual or potential, direct or indirect, contact with any chemical and biological agent, or physical and safety condition" (11).

**Data indicate that new chemical substances are generated at the rate of about 8 percent annually and 5 percent of existing chemicals are discontinued, resulting in an assumed annual growth rate of 3 percent (3,12).

***47 Fed. Reg. 12092, 12108 (1982).

Photo credit: Occupational Safety and Health Administration

Special clothing protects worker's skin and respiratory tract from exposure to toxic chemicals

Ionizing radiation

Ionizing radiation is energy in the form of waves or particles that produces certain charged particles known as ions in passing through matter. It may harm exposed individuals or their unborn children. For the exposed individual, the principal risk is that he or she may develop cancer. Radiation-induced cancers include leukemia and most of the commonly occurring solid cancers. Other possible adverse effects of ionizing radiation include eye cataracts, nonmalignant skin damage, blood disorders, and impaired fertility. Unborn children can be harmed in two ways. The first is through radiation-induced adverse changes in the genetic material from their parents, which can be passed on to future generations. The second is by direct in utero exposures which can result in birth defects, growth retardation, or cancer (4).

Occupational exposures to ionizing radiation occur in many fields. In the health professions, for example, exposures result from the use of medical and dental X-rays and radiopharmaceuticals. In industry, exposures result from the use of X-rays and gamma rays for flaw detection and other testing of materials. In the production and use of nuclear energy, exposures occur for miners, fuel processors, material handlers, and others. Radium workers and research laboratory workers often are exposed to ionizing radiation.

Estimates vary on the number of workers potentially exposed to ionizing radiation. The Environmental Protection Agency estimated that 1.1 million workers were potentially exposed in 1975 (4).* The Committee on the Biological Effects of Ionizing Radiation estimated that approximately 750,000 workers each year were potentially exposed, based on exposure data for different groups in different years between 1969 and 1977 (8).

Control of occupational health hazards

To prevent occupational disease, health hazards must be recognized, evaluated, and controlled.

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*Workers exposed in mining operations were not included in these estimates; there is little information on exposure of such workers with the exception of underground uranium miners.

Environmental and biological monitoring, engineering controls, personal protective measures, and modified work practices are the techniques used to accomplish this goal (1). Genetic testing is just one of many techniques that fall into these general categories. It could complement but probably not replace any of the existing techniques.

Recognition and evaluation of hazardous substances or agents involves identification of potential hazards in the workplace and determination of the degree of exposure. The two major complementary ways to do this are through environmental and biological monitoring (1). Environmental monitoring uses various sampling instruments or personal monitoring devices to identify hazardous substances in the environment and to determine their concentration (1). Biological monitoring uses biochemical and other tests on body fluids, tissues, expired air, or human wastes to estimate the amount of a hazardous substance actually absorbed by a particular worker as well as its health effects (7). Some genetic testing techniques are a type of biological monitoring.

Control of hazardous substances and their effects may be accomplished by engineering techniques designed to lower or eliminate exposure or by measures designed to protect individual workers (1). Engineering controls include the substitution of a less harmful material for a hazardous one, the alteration of a process to lower the degree of exposure, the isolation or enclosure of a process to lower the degree of exposure, the use of exhaust systems, and ventilation with clean air (1). Measures targeted to individuals include personal protection devices such as respirators or special clothing and workplace practices such as job placement in a suitable environment, job rotation to minimize exposure, and job denial (1).

The use of personal protective measures requires the identification of individuals or groups who can benefit from them. Such identification is the goal of medical surveillance, a preventive activity using preemployment or periodic medical examinations both to identify individuals or groups that may be predisposed to some occupational illnesses and to monitor the health experience of workers exposed to presumably safe levels of potentially hazardous substances (7). Genetic testing has potential for use in medical surveillance.

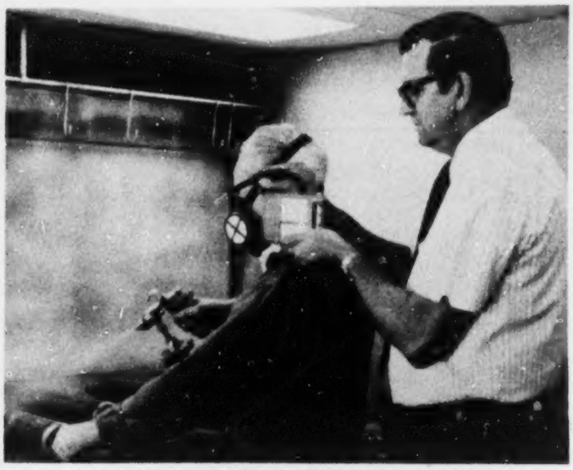

Photo credit: Occupational Safety and Health Administration

Environmental monitoring

Photo credit: Occupational Safety and Health Administration

Personal protection mask is utilized to safeguard workers in many occupations where hazardous substances are present

Genetic testing

Theoretical foundations: biological diversity and differential susceptibility

Genetically determined individuality is a fact of life. People differ not only in such obvious physical characteristics as height, facial features, and skin color, but also in ways that can only be determined in a laboratory, such as blood type and types of proteins found in blood plasma. Variations in some characteristics or traits result from the interaction of many genes; variations among other traits result from variations in a single gene that controls that trait. On the basis of a mere two dozen traits that have been extensively studied, some scientists have calculated that the probability of any two people (except identical twins) being exactly alike is roughly 1 in 4 billion (15).*

Genetic variability is also a factor in the different reactions of people to environmental factors, including disease-causing agents such as bacteria, viruses, and chemicals. There is evidence that some people are at a higher risk than others of contracting diseases—cancer and heart disease, for example—not only because of environmental factors such as diet or smoking, but because of their genetic makeup (5,6). In fact, there are a few cases where a person's genetic makeup has been proven to predispose him or her to certain illnesses in the presence of some environmental factor. One situation involves a deficiency in the enzyme glucose-6-phosphate dehydrogenase (G-6-PD). The production of this enzyme is controlled by a single gene; some people have a variant form of that gene that results in a deficiency in the enzyme. The deficiency generally causes them no harm. However, if they take certain antimalarial drugs or eat a type of bean known as the fava bean, they may suffer from acute anemia (16). Thus, G-6-PD deficient individuals are at a higher risk of illness than other people when exposed to those environmental stresses.

Many factors besides genetic makeup can cause an individual to be predisposed to illness triggered by environmental factors. Among these are age, sex, nutritional status, lifestyle, and prior exposure to the environmental factors.

Prior exposure is particularly important for the purposes of this report. If the environmental factor is a chemical, it may be in the body at levels where only slight additional amounts could cause illness. In fact, the prior exposure may already have begun the disease process even though the disease itself may not appear for many years.

These considerations lead to the concept in occupational medicine of unequal risk. Individuals or groups that may be predisposed to illness have been called, among other terms, "hypersusceptible," "high-risk," and "sensitive." These terms often have been used interchangeably but also have been defined by different experts in different ways.

This report uses the terms "increased risk," "genetically predisposed," and "susceptible." When applied to individuals or groups, the terms "increased risk" or "susceptible" refer to a higher probability than average of developing a condition, illness, or other abnormal status. In the context of genetic testing, this increased risk may result from either inherited genetic traits or previous exposure to environmental insult. The term "genetically predisposed" refers to the situation where one or more of an individual's inherited genetic traits may cause him or her to be at an increased risk of illness when exposed to some environmental stresses.

Detection of individuals or groups at increased risk

Genetic testing, as used in this report, applies to several techniques used to examine workers for particular inherited genetic traits or environmentally induced changes in their genetic material on the assumption that the traits or changes may predispose them to illness. It has been used by some manufacturing companies and utilities in both medical practice and research. There are two inherently different kinds of testing, genetic monitoring and genetic screening (fig. 1).

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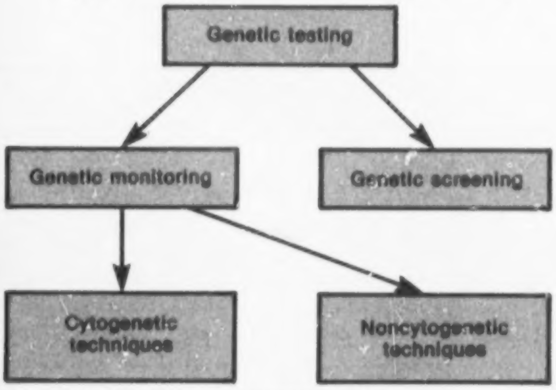
*Another approach to the question of human variability is to look at the number of nucleotides in the human genome, which is about 10^9. On this basis, the chances of two people being exactly alike is 1 in 10^{18} ($10^9 \times 10^9$).

Genetic monitoring is done to assess whether or not genetic damage has occurred in certain cells of an individual as a result of exposure to hazardous chemicals or ionizing radiation. Monitoring can also be done over a period of time to look for responses to variations in exposure. Thus, it can be used to measure genetic changes in certain cells from before exposure through various levels of exposure. Monitoring can be done in one of two ways. Cytogenetic techniques look for damage to the gross structure of chromosomes, the cellular structures that contain the genetic material, deoxyribonucleic acid (DNA). Noncytogenetic techniques look for damage to the actual molecular structure of DNA. For the most part, these latter techniques are still in a developmental stage.

Genetic monitoring involves examining blood and other body fluids for evidence of genetic damage to cells from chemicals or ionizing radiation. This damage may indicate exposure to a hazardous agent and the possibility that the group so exposed will be at an increased risk of developing diseases, particularly cancer. Thus, this procedure has potential as an early warning system, by indicating that exposures to known or suspected carcinogens are too high or that a previously unsuspected chemical should be viewed as a potential carcinogen.

Figure 1.—Components of Genetic Testing



SOURCE: Office of Technology Assessment.

In contrast, genetic screening is a one-time testing process to determine the presence of particular genetic traits, regardless of whether the person has been exposed to a hazardous substance (9). Some genetic traits appear to predispose an individual to adverse health effects in the presence of a particular chemical. While normally not harmful, the traits may make the individual susceptible to hemolytic chemicals, pulmonary irritants, oxygen deprivation, or other physical or chemical stresses in the workplace. For example, two scientists proposed in 1963 that workers in the chemical industry be tested for G-6-PD deficiency on the grounds that 37 chemicals or families of chemicals may cause such employees to develop anemia (20). Most screening tests require that blood be drawn for laboratory tests.

In sum, screening is used to determine individual susceptibility, whereas monitoring may be able to assess a chemical's effect on an exposed population in order to determine if that population is at increased risk. Because of this distinction, one use of screening could be to exclude genetically susceptible individuals from jobs where they would be exposed to hazardous substances, whereas monitoring would most likely indicate a need to lower exposure levels for a group identified to be at increased risk.

Genetic monitoring must be subjected to two principal technical questions: Are the techniques used to assess genetic damage reliable and valid? Is there an association between positive test results and an increased risk of disease? Similarly, the reliability and validity of screening tests are important technical questions, but the key question here is whether or not there is an association between the genetically determined trait and any increased susceptibility of that individual to harm from particular chemicals.

When used as described here, screening and monitoring are forms of medical practice. They can also be used in medical research. It is important to distinguish between medical practice and medical research because different legal and ethical principles can govern each, depending on the situation. The term "practice" generally refers to medical interventions that are designed solely to enhance the well-being of an individual and that have a reasonable expectation of success. The

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purpose of medical practice is to provide diagnosis, preventive treatment, or therapy to individuals. Research, on the other hand, refers to an activity designed to test a hypothesis so that conclusions may be drawn. Its purpose is to contribute to a general body of knowledge, expressed in the form of theories, principles, and statements of relationships (10). Medical research is often done to determine the value of new techniques for medical practice. It generally does not enhance the well-being of the individual, and, in fact, may have some risks associated with it.

Potential benefits and risks of genetic testing

Advocates of genetic testing believe it might be able to play an important role in the prevention of occupational disease. By identifying workers who may be at increased risk of disease because of past or potential exposure to hazardous substances, additional preventive measures could be taken by the company or the workers themselves. In addition to the obvious and significant benefits of preventing serious illness, there could be indirect benefits, such as a reduction in the costs associated with occupational disease for employers, employees, and society. These costs include medical, insurance, and legal expenses; time lost from work; and disability or unemployment payments.

The use of this emerging technology, however, raises several questions. Are the techniques sufficiently developed so as to predict reliably an association between either genetic damage or a person's genetic makeup and disease? Since many of the genetic traits sought in screening are found disproportionately among some races and ethnic groups, could the use of the tests result in discrimination on the basis of race, sex, or national origin? How will the availability of the tests affect the employer's responsibility for maintaining a safe workplace? How might these procedures affect efforts to reduce the level of hazardous substances in the workplace? If the tests are shown to be effective, to what degree should society protect high-risk individuals or groups, at what cost, and who should bear that cost?

Organization and scope of report

This report attempts to assess the potential risks, benefits, and effects of genetic testing. Part I discusses the extent of testing on the basis of a survey of major companies and unions conducted by OTA. Part II explains the underlying scientific principles. Part III assesses the current state of the technology and expected future developments. It addresses the question of whether the technology in fact could play a role in reducing occupational disease. Part IV analyzes the legal, ethical, and economic issues raised by this technology. It considers whether genetic testing is compatible with law or established ethical principles and how the costs and benefits of the technology could be assessed. Part V integrates the findings of the previous parts into a discussion of issues and policy options for possible congressional action.

The report does not consider certain aspects of genetic testing. Hazards to offspring are not addressed; the report considers only the risk to the workers themselves. The report also does not assess many of the claimed risks of the widespread use of this technology. Because genetic testing is an emerging technology, little evidence exists concerning its potential impacts. Finally, it was not within the scope of this study to assess whether occupational exposures to hazardous substances are at "safe" levels and whether other technologies might be more appropriate for preventing occupational diseases.

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Survey of the Use of Genetic Testing in the Workplace

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Chapter 3

Survey of the Use of Genetic Testing in the Workplace

There have been conflicting accounts of the extent of genetic testing and the use of its results. In testimony given before Congress in the fall of 1981, the corporate medical director of a large chemical company stated that except for sickle cell trait tests, his company " . . . is not conducting genetic screening of its employees, and I am not aware of any other company which is" (2). However, a series of articles in the New York Times in February 1980 alleged a widespread corporate practice of such testing on American workers (3). Furthermore, a May 1981 survey of east coast industrial physicians indicated that preemployment, preplacement, and periodic testing for sickle cell anemia, hemoglobin disease, and glucose 6-phosphate dehydrogenase (G-6-PD) deficiency was being conducted in some large east coast companies (1).

None of these or other accounts examined by OTA has been based on a rigorous, scientifically valid assessment of the use of genetic testing. Therefore, in an attempt to dispel the confusion and speculation and to provide necessary data for policy analysis, OTA surveyed major U.S. industrial companies, utilities, and unions about their use of this technology.

Purpose

The survey was designed to determine:

- the frequency of past, present, and anticipated genetic screening and cytogenetic monitoring* in the workplace and whether they had been conducted on a routine, special, or research basis;
- which tests were used and under what circumstances;
- how the results of the tests were used; and
- the criteria against which tests have been measured to determine acceptability for use.

The survey did not attempt to establish the number of workers involved in these tests; that information would have required a much more extensive effort.

Study design

The survey was conducted for OTA from February 25 to June 8, 1982, by the National Opinion Research Center (NORC), a nonprofit survey research corporation affiliated with the University of Chicago. NORC sent confidential questionnaires to the chief executive officers of the 500 largest U.S. industrial companies,* the chief executive officers of the 50 largest private utility companies,** and the presidents of the 11 major unions that represent the largest numbers of employees in those companies.*** For further information on the study design and other aspects of survey methodology, see appendix A. The NORC report to OTA on the survey is in appendix B.

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*The questionnaire used the term biochemical genetic testing to refer to genetic screening and the term cytogenetic testing to refer to cytogenetic monitoring.

*Identified by Fortune 500 listing of U.S. companies engaged in manufacturing/mining; *Fortune*, vol. 103, No. 9, May 4, 1981.

**Identified by Fortune Magazine List C; *Fortune*, vol. 103, No. 9, May 4, 1981.

***Identified in Directory of National Unions and Employees Association (1979) by the U.S. Department of Labor.

By the June 8, 1982, cutoff date, 366 organizations had answered the questionnaire, a 65.2 percent response rate, and 26 organizations had specifically declined to do so, a 4.6 percent refusal rate. Those who declined generally gave either no reason for refusal or the reason of corporate policy not to respond to surveys. (See table 1.)

Table 1.—Frequency of Response to Survey by 6/8/82 By Type of Response (based on 561 organizations)

Type of response	Number	Percent
Participated	366	65.2%
Refused to participate:	26	4.6%
Policy not to reply to surveys	(10)	
Not interested, no time	(3)	
Object to methodology	(1)	
Phone refusal—no reason	(12)	
Unknown	169	30.1%
Total	561	

SOURCE: National Opinion Research Center, survey conducted for OTA, 1982.

Results

Overall rates of testing

Of the 366 organizations responding, 6 (1.6 percent) were currently conducting genetic testing,* 17 (4.6 percent) used some of the tests in the past 12 years, 4 (1.1 percent) anticipated using the tests in the next 5 years, and 55 (15 percent) stated they would possibly use the tests in the next 5 years. Most of these organizations are in manufacturing/mining (particularly chemicals) or are utility companies. Of those organizations that have tested in the past 12 years, five are currently doing so. (See table 2.) Because the questionnaire instructed respondents to include any instance of testing, positive responses can include isolated instances of testing as well as long-term testing programs. Among the six companies currently testing, two are in the chemical industry, two are utilities, and two are in the electronics industry. Half of those that tested in the past are chemical companies. Of the four organizations that anticipate the use of genetic testing, two are conducting testing at present, one has done so in the past, and one has never had such a program. None of the four responding unions reported any testing. These results are set forth in more detail in tables 3, 4, and 5.

Table 2.—2 x 2 Contingency Table for Organizations Engaged in Genetic Testing (past testers by current testers)

		Past testers		
		Yes	No	Total
Current testers	Yes	5	1	6
	No	12	348	360
	Total	17	349	366

SOURCE: National Opinion Research Center, survey conducted for OTA, 1982.

Types of testing: genetic screening and cytogenetic monitoring

Organizations that reported some genetic screening were asked whether they had ever tested employees for genetic traits associated with: (A) any red blood cell and serum disorders, (B) liver detoxification systems, (C) immune system markers, or (D) heterozygous chromosomal instabilities. For each of the four broad categories A through D, the questionnaire listed several examples. Of those who have ever tested, 14 of the organizations had tested in category A, 3 in category B, 5 in category C, and none in category D. Organizations that have used red blood cell and serum disorder tests, category A, often used more than one type of test. The most frequently used test in this category was that for sickle cell trait, for which 10 organizations have tested. The G-6-PD and serum alpha-1 antitrypsin deficiency tests were the second most frequently used. (See table 6 for a summary of the frequency of individual genetic screening tests.)

For each test, companies were asked about the circumstances under which the tests were done (that is, routinely, for research, or for other reasons) and the type of employee tested. Respondents generally said they tested routinely or for unspecified reasons. (See table 6.) Employees most often were selected on the basis of ethnicity and race for sickle cell trait testing and on the basis

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*Genetic screening and/or cytogenetic monitoring.

Table 3.—Distribution of Organizations By Type, Indicating Current, Past, and/or Future Use of Genetic Testing (based on 366 responses)

	Testing					
	Current		Past		Future	
Organization type (number of respondents)	Yes	No/NA[a]	Yes	No/NA[a]	Yes/Poss.	No/NA[a]
Manufacturing/mining companies (322)	4	318	16	306	49	273
Private utility companies (31)	2	29	1	30	9	22
Unions (5)	0	5	0	5	0	5
Unknown (8)	0	8	0	8	1	7
Total (366)	6 (1.6%)	360	17 (4.6%)	349	59 (16.1%)	307

[a] A combination response. Further breakdown is impossible since the category (current, past, future) is a summary of responses to two questions dealing with genetic screening and cytogenetic monitoring. In the case of No/NA, most responses were No; for Yes/Poss., most responses were possibly. See table 4 for further breakdown.

SOURCE: National Opinion Research Center, survey conducted for OTA, 1982.

Table 4.—Frequency of Current, Past, and/or Future Use of Genetic Testing, By Type (based on 366 responses)

	Testing									
	Current			Past			Future			
Type of test	Yes	No	N/A	Yes	No	N/A	Yes	Poss.	No	N/A
Genetic screening	5	350	11	12	342	12	1	53	292	20
Cytogenetic monitoring	2	354	10	6	348	12	3	49	294	20

SOURCE: National Opinion Research Center, survey conducted for OTA, 1982.

Table 5.—Distribution of Companies by Classification,[a] Indicating Current, Past, and/or Future Use of Genetic Testing (based on 366 responses)

	Genetic testing					
	Current		Past		Future	
Main industrial classification (number of respondents)	Yes	No/NA[b]	Yes	No/NA[b]	Yes/Poss.	No/NA[b]
Chemical (37)	2	35	8	29	11	26
Utilities (33)	2	31	1	32	10	23
Petroleum (18)	0	18	0	18	4	14
Pharmaceuticals (9)	0	9	0	9	3	6
Rubbers/plastics (4)	0	4	0	4	3	1
Metals (16)	0	16	0	16	2	14
Others (249)	2[c]	247	8	241	26	223
Total (366)	6 (1.6%)	360	17 (4.6%)	349	59 (16.1%)	307

[a] Main industrial classification based on the first listed response of respondent to question concerning the major industrial classification of their company.

[b] A combination response. Further breakdown impossible since the category (current, past, future) is a summary of two questions: 1) genetic screening, 2) cytogenetic monitoring. In the case of No/NA, most responses were No; for Yes/Poss. most responses were possibly. See table 4 for further breakdown.

[c] Both of these companies report electronics as their main industrial classification.

SOURCE: National Opinion Research Center, survey conducted for OTA, 1982.

of job category for other types of tests. No organization reported basing a genetic screening test on an employee's sex. (See table 7.)

Of the organizations that reported cytogenetic monitoring, four had tested for chromosomal aberrations and two for sister chromatid exchanges (SCE). None reported having tested for mutations by assaying either deoxyribonucleic acid (DNA) or enzymes. Most frequently, no reason was given for chromosomal aberration testing. The two companies that did SCE testing said it was for research purposes. (See table 6.) Job category was the only employee-related characteristic used to determine who would be tested. (See table 7.)

Table 6.—Genetic Testing Ever[a] Conducted By Purpose and Type of Test (based on 18 responses)

	Genetic screening							Cytogenetic monitoring	
Purpose	Sickle cell	G-6-PD	SAT	Methemoglobin reductase	Unspecified red blood cell/serum disorder	Unspecified liver detox	Unspecified immune system markers	Chromosomal aberrations	Sister chromatid exchanges
Routine . . .	5	3	1	0	1	1	4	1	0
Research . .	1	0	2	1	2	1	0	1	2
Other	6	2	2	1	2	1	3	3	0
Total number of respondents utilizing test[b]	10	4	4	1	3	3	5	4	2

[a] In the past 12 years.
[b] Since categories above are not mutually exclusive, total can be less/more than sum of categories.

SOURCE: National Opinion Research Center, survey conducted for OTA, 1982.

Table 7.—Genetic Testing Ever[a] Conducted By Criteria and Type of Test (based on 18 responses)

		Genetic screening						Cytogenetic monitoring	
Criteria	Sickle cell	G-6-PD	SAT	Methemoglobin reductase	Unspecified red blood cell/serum disorder	Unspecified liver detox	Unspecified immune system markers	Chromosomal aberrations	Sister chromatid exchanges
Job category	1	2	2	0	2	1	1	2	1
Ethnicity/race	7	0	0	0	0	0	0	0	0
Sex	0	0	0	0	0	0	0	0	0
Total number of respondents utilizing test[b]	10	4	4	1	3	2	4	4	2

[a] In the past 12 years.
[b] Since categories above are not mutually exclusive, total can be less/more than sum of categories.

SOURCE: National Opinion Research Center, survey conducted for OTA, 1982.

Recipients were asked about the factors considered in the decision to implement testing and the criteria employed in selecting specific tests. Data from epidemiological studies, data from animal studies, and other reasons such as employee protection were the highest ranked factors involved in decisions to implement genetic testing for both genetic screening and cytogenetic monitoring. (See table 8.) The predictive value of a test, its specificity, scientific consensus, and other factors such as research findings were the factors cited most frequently as criteria for selecting a specific genetic test. These responses were similar for both genetic screening and cytogenetic monitoring. (See table 9.)

Table 8.—Genetic Testing Ever[a] Conducted By Reasons for and Type of Testing (based on 18 responses)

	Type of testing	
Reasons for deciding to implement testing	Genetic screening	Cytogenetic monitoring
Data epidemiologic studies	6	2
Data animal studies	4	2
Legal consequences of not testing	3	0
Union employee initiative .	3	0
Cost-benefit analysis	2	0
Other[b]	4	3

[a] In the past 12 years.
[b] Includes reasons related to protecting employees, research findings.

SOURCE: National Opinion Research Center, survey conducted for OTA, 1982.

The types of testing carried out by current testers were compared with those of past testers. For genetic screening, current testers are using a slightly greater variety of tests (tests for red blood cell and serum disorders, liver detoxification systems, and immune system markers) than

Table 9.—Genetic Testing Ever[a] Conducted By Criteria for Test Selection and Type of Testing (based on 18 responses)

	Type of testing	
Criteria[b]	Genetic screening	Cytogenetic monitoring
Predictive value of test[c] . . .	5	1
Specificity of test[d]	5	1
Scientific concensus	4	2
Sensitivity of test[e]	3	0
Cost of test	2	0
Other[f]	4	3

[a] In the past 12 years.
[b] A respondent may have based its selection for a test on one or more of the above criteria.
[c] Predictive value of test: the likelihood that the disease status of the individual will be correctly identified by the test; i.e., a disease-free individual will have negative test result, a diseased individual will have positive test result.
[d] Specificity of test: ability of test to correctly identify individuals without disease.
[e] Sensitivity of test: ability of test to correctly identify individuals with disease.
[f] Includes research findings (general).

SOURCE: National Opinion Research Center, survey conducted for OTA, 1982.

past testers and at a slightly higher proportion of usage. Of the six current testers, five are testing for red blood cell and serum disorders, three for liver detoxification systems, and two for immune systems markers. Eight of twelve past testers had tested for red blood cell and serum disorders, none had tested for liver detoxification systems, and two had tested for immune system markers. In fact, however, because of the small numbers involved, the only notable difference between current and past testers may be the current use of tests for liver detoxification systems. In any event, testing for red blood cell and serum disorders continues to be the most frequently used test. (See table 10.)

A different pattern of use emerges for cytogenetic monitoring. Of the six current testers, one is testing for chromosomal aberrations and one is testing for sister chromatid exchanges. For the 12 past testers, 3 tested for chromosomal aberrations and 1 tested for sister chromatid exchanges. This may reflect the change in the state of the art concerning the science of sister chromatid exchanges. (See table 10.) In any event, the number of tests remain small and caution is advised in interpreting these data.

Actions taken as a result of testing

Responses concerning the way in which the results of genetic screening or cytogenetic monitoring were used varied greatly, ranging from actions involving an employee to changing or discontinuing a product. Of the 18 companies that reported taking some action, 8 reported that they had informed an employee of a potential problem. Five respondents reported transferring the "at-risk" employee. Two suggested that the employee seek another job as a result of testing. One discontinued or changed a product. The complete list of actions taken appears in table 11.

Generalizability of the survey

Can the results of this survey be generalized to the population of Fortune 500 companies, large utility companies, and major unions? An answer to this involves two additional questions: Are the responses equally distributed among the groups

Table 10.—Distribution of Type of Testing By Status of Tester (based on 18 responses)

	Status of tester						
	Current N-6			Past N-12			
Type of testing	Yes	No/NA	Percent using	Yes	No/NA	Percent using	Total
Genetic screening:							
Red blood cell and serum disorders	5	1	83%	8	4	67%	18
Liver detoxification systems	3	3	50%	0	12	0%	18
Immune system markers	2	4	33%	2	10	10%	18
Heterozygous chromosomal instabilities	0	6	0%	0	12	0%	18
Cytogenetic monitoring:							
Chromosomal aberrations	1	5	17%	3	9	25%	18
Sister chromatid exchange	1	5	17%	1	11	8%	18
Mutations by assaying DNA	0	6	0%	0	12	0%	18
Mutations by assaying enzymes	0	6	0%	0	12	0%	18
Other	1	5	17%	0	12	0%	18

SOURCE: National Opinion Research Center, survey conducted for OTA, 1982.

Table 11.—Actions Taken by Respondents That Have Ever[a] Used Genetic Testing (based on 18 responses)

Type of action[b]	Number of companies
Informed employee of a potential problem	8
Transferred employee	5
Personal protection device	3
Other action	3
Suggested employee seek other job	2
Installed engineering control	2
Implemented research program	1
Discontinued/changed product	1

[a] In the past 12 years.
[b] A respondent may have taken more than one action.

SOURCE: National Opinion Research Center, survey conducted for OTA, 1982.

represented in the survey? Are characteristics of the respondents different from the nonrespondents? These two questions are discussed in turn.

By the close of the survey, a discrepancy in response rate among the groups represented in the survey became apparent. The large corporations had the highest response rates: 68 percent for utilities and 61.5 percent for the top 200 companies in the Fortune 500 listing; the unions and small corporations had the lowest response rates: 36.4 percent for unions and 44 percent among the bottom 300 companies in the Fortune 500 listing. (See app. A.) The variation in response pattern was most probably due to the followup efforts that focused on the top 100 companies of the Fortune 500 listing and organizations in selected industrial classifications such as utilities. Thus, the results of this survey may be more applicable to the larger manufacturing/mining and utility companies than to smaller manufacturing/mining companies and unions.

Analysis of selected characteristics of respondents compared with nonrespondents is limited to the Fortune 500 companies. Respondents and nonrespondents were compared on the following characteristics: geographic location, size of organization, and type of industry. Rates of response and nonresponse did not differ greatly geographically. (See app. A.)

For size of company, however, the rate of nonresponses did differ widely from the rate of responses. For example, 53 percent of the nonrespondents were in the smallest companies, compared with 32 percent of the respondents. Again, because larger companies were used in followup efforts, the response rates may reflect these efforts. (See app. A.)

Rate of nonresponse did not vary greatly from rate of response with respect to industry classification. Eleven industries had a slightly higher rate of response than predicted. Of these industries, five (chemicals, petroleum refining, rubber and plastic products, metal manufacturing, and pharmaceuticals) were the key industries selected for followup activities and the rates from the remaining six (glass/concrete, electronics, measuring equipment, motor vehicles, aerospace, and office equipment) may be explained by such factors as the effect of followup based on size of company or chance. (See app. A.)

Thus, the results of the survey may be more representative of the larger manufacturing/mining corporations and private utility companies as identified in Fortune magazine listings; however, the respondents do not appear to differ greatly from the nonrespondents in geographic location or type of company.

Comments on survey

Respondents were encouraged to write explanatory notes or other comments on the questionnaires and on the post cards. Thirty-one respondents did so. (See app. C for complete text of comments.) Three current testers sent in comments. Two of these respondents said testing was being done for reasons of health evaluation—preplacement and/or routine monitoring; one respondent said that such testing should not be interpreted to mean a large-scale testing program or a problem exists.

Comments were received from two companies that had tested in the past. Both respondents referred to testing for sickle cell trait, one at the request of the State health department, and the other at the request of the employer for employees of child-bearing age as part of the company's preventive medical program.

Seven organizations that anticipate future testing but that have not conducted any testing to date provided comments. The comments ranged from addressing animal research to questionnaire improvement to any future testing being dependent on "practical utility."

Comments received from 19 organizations that have never tested or that do not plan to test in the future focused on three major points. The first was the genetic testing was not relevant to the products or processes to which their workers were exposed. The second was that these tests were not sufficiently developed for use. The third point was that the organization was satisfied with its current conventional industrial hygiene practice and standard medical surveillance of its workers.

Caveats

In evaluating the results of the survey, several caveats must be considered. First, since the questionnaire instructed respondents to include any instances of testing, positive responses can include isolated cases as well as long-term testing programs. Second, the questionnaire was not structured to provide information on the number of workers tested. Positive responses indicate only the existence of testing, not its extent. Third, since approximately one-third of the population did not respond and the number of organizations testing is very small, any generalizing of these results to the study population as a whole is not warranted. Fourth, the level of effort employed in completing each questionnaire is unknown. For example, holding companies which have autonomously operating subsidiaries may or may not have included the activities of those subsidiaries in their responses. Fifth, a limitation of an anonymous questionnaire is that respondents cannot be contacted about missing information or unclear responses. Approximately 3 percent of the respondents failed to answer every item in the core questions. Eight returned questionnaires did not provide enough information to allow the respondents to be classified as a Fortune 500 company or as a utility. Sixth, the use of post cards for followup has pitfalls: respondents may return post cards but not questionnaires or vice versa; NORC received 293 post cards and 366 questionnaires. This may have resulted in duplication of information or minimized the effect of followup.

Conclusions

The survey of major U.S. industrial companies, utilities, and unions has shown that genetic testing currently is being used by a few companies, that its use has declined in the past 12 years, but that it may be used by many more companies in the future. The responses cannot be generalized to the survey population or to all U.S. companies and labor unions. However, it is clear that 17 organizations have used genetic testing in the past 12 years, 5 of the 17 and 1 other currently are doing so, and 59 organizations have expressed an interest in using these tests. None of these organizations is a union. The extent of testing by these organizations is unknown.

Further, of the 18 companies that have ever conducted genetic testing in the past 12 years, more companies have conducted genetic screening (17 companies) than cytogenetic monitoring (8 companies). Tests for sickle cell trait were the most frequently used type of genetic screening and tests for chromosomal aberrations were the most frequently used type of cytogenetic monitoring. Research was the least frequently mentioned purpose for testing. Respondents generally tested routinely or for other unspecified reasons. The type of employee chosen for testing was based most often on ethnicity and race for sickle cell trait testing, and job category for other types of tests. Sex was never stated as a criterion used in determining the test of choice. Actions taken on the results of the tests ranged from informing the employee of a potential problem (eight companies) to discontinuing or changing the product (one company).

Data from epidemiological and animal studies were the most frequently cited factors in the decision to implement testing of those companies that tested. A cost-benefit analysis was the least important factor. The predictive value and specificity of a test were the most important criteria in the selection of the specific genetic screening test, while research findings were most important in the selection of the specific cytogenetic monitoring test.

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Part II

Underlying Scientific Principles

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Chapter 4

Essentials of Genetics

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Chapter 4

Essentials of Genetics

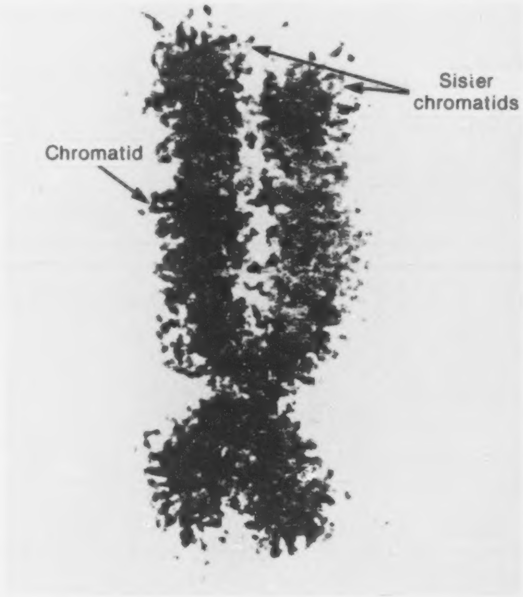
The role of genes in disease is still not fully understood. Many diseases—cancer and heart disease, for example—appear to have some genetic influence. These genetic variations may be inherited or may arise from environmental sources. In other cases, it is hypothesized that a person with inherited types of gene variations may suffer harmful effects when exposed to hazardous substances.

The occupational studies assessed in Part III of this report rely on genetic analyses. An understanding of genetics—the basic structure and function of genes and their connection with disease—will enable the reader to comprehend more readily the report's interpretation of those studies. This chapter, therefore, attempts to provide an introduction to the complex subject of genetics.

Chromosomes

In higher organisms, the nucleus of each cell contains the genetic material DNA (deoxyribonucleic acid), which directs all the functions of the cell such as metabolism and growth. The DNA in its normal state in the nucleus is joined with proteins to form a set of complicated structures called chromosomes. Each human cell contains 46 chromosomes, half derived from the mother and half from the father. These 23 pairs of chromosomes mean that all genetic material is represented twice in each cell. One of the twenty-three pairs is a pair of sex chromosomes. Females have two X chromosomes and males have one X and one Y. When the cell is in a resting stage, all the chromosomes are tangled and difficult to distinguish; just prior to cell division, however, the chromosomes condense and replicate to appear in a light microscope as dual structures, each chromosome consisting of two identical chromatids (fig. 2). These two sister chromatids are held together by a central constriction, the centromere. At cell division, the sister chromatids are pulled apart at the centromere, and one chromatid goes to each of the two daughter cells, thus ensuring a full complement of DNA in each cell.

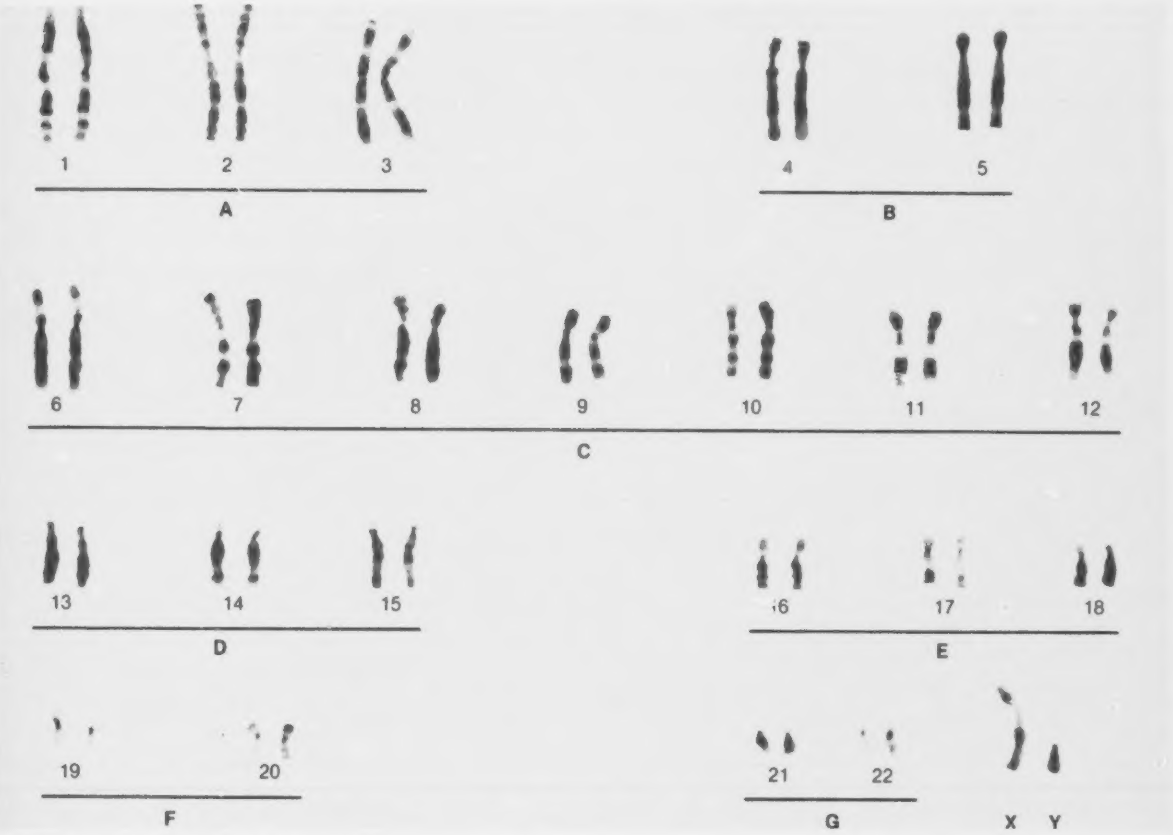
Figure 2.—A Chromosome



SOURCE: Office of Technology Assessment.

Each of the 23 pairs of chromosomes is a unique size and shape, permitting the chromosomes to be distinguished from one another. In addition, various staining treatments have been developed that reveal, for each chromosome, a characteristic sequence of "bands" composed of alternately dark and light staining regions. From the combination of size, shape, and banding patterns, the 46 chromosomes from a single cell can be arranged into a systematic picture called a karyotype (fig. 3). Chromosomal abnormalities, which alter the

Figure 3.—Normal Human Male Karyotype



SOURCE: Cytogenetics Laboratory, The Johns Hopkins University.

banding patterns or size or shape, can be detected using this technique.

The study of cytogenetics compares the appearance of the chromosomes in the karyotypes to identifiable traits in the individual. Several chromosomal abnormalities have been identified, and they fall into two classes: a change in the number of chromosomes and a change in the chromosome structure. Changes in the number of chromosomes occur during germ cell (egg or sperm) formation and are detected in the offspring. For example, Down's syndrome is a result of an extra chromosome 21 in all cells. Although it is possible for the number of chromosomes to change in somatic cells (all cells other than germ cells) by a mistake made during cell division, these cells are usually nonviable; thus, this type of change will not be discussed further.

Chromosomal aberrations, or changes in chromosome structure, can occur spontaneously or can be caused by chemicals or ionizing radiation. They are important because, whatever their origin, they can be replicated and passed on to succeeding generations of somatic cells. How chemicals or ionizing radiation causes these aberrations is not well understoood.

Everyone has some chromosomal aberrations in his or her somatic cells. In lymphocytes (white blood cells) grown under laboratory conditions, roughly 2 out of every 100 cells contain at least one structurally abnormal chromosome. Similar levels of aberrations have been seen in preparations of bone marrow cells and fibroblasts (connective tissue cells) and presumably are present to some extent in every kind of somatic cell (see app. D). These "background" or "spontaneous"

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chromosomal aberrations are thought to be the consequence either of failure to repair rare replication errors or of postreplication chromatid exchanges, which may be a normal part of the cell cycle. However, an increase in the number of aberrations may imply the existence of certain rare chromosomal instability diseases (discussed below) or exposure to clastogens (chromosome-damaging agents) in the environment. In the latter case, such an increase may serve as a method for monitoring exposure to harmful agents.

Another type of chromosomal change is a sister chromatid exchange (SCE). SCEs are exchanges of apparently equivalent sections of the sister chromatids of the same chromosome (fig. 4). This phenomenon, which can be seen only under special laboratory conditions, occurs at a much higher frequency than do chromosomal aberrations, with most reported background frequencies being in the range of 5 to 15 SCEs per cell (see app. E).* The biological or genetic significance of SCEs is unknown. While the presence of SCEs in a cell is not necessarily indicative of damage to that cell, some empirical evidence suggests a relationship between SCEs and agents which damage DNA (7). The detection of SCEs thus is seen as another way to monitor damage to chromosomes. A major exception is that SCEs are not usually induced by ionizing radiation (3).

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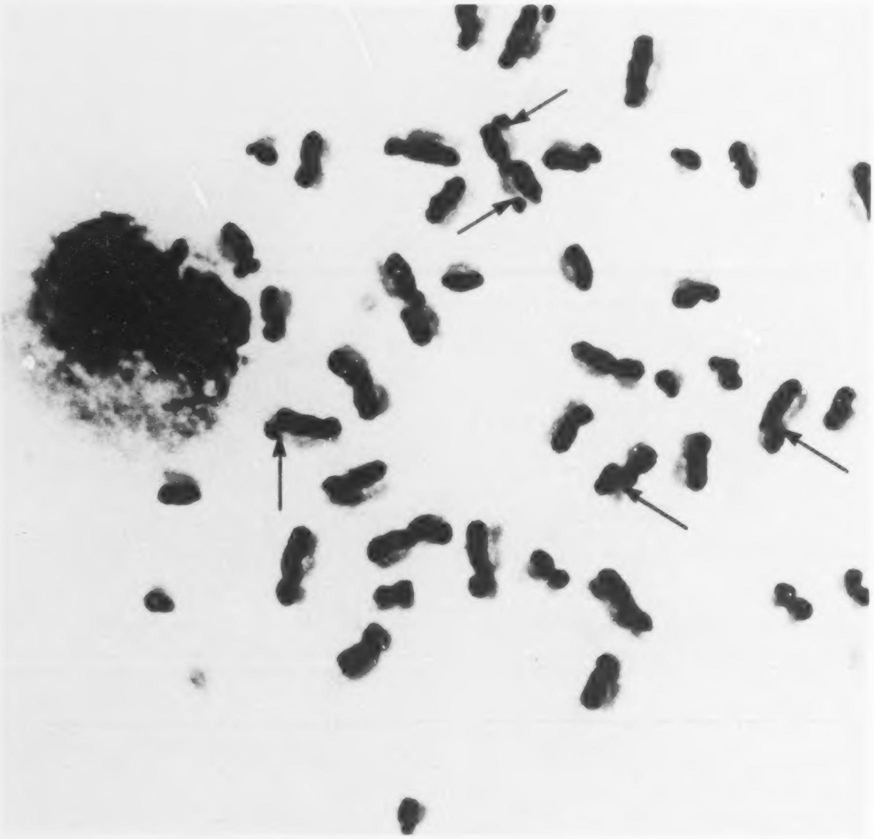
*These higher background frequencies are thought to be due to the laboratory procedures necessary for visualization of SCEs.

Figure 4.—Sister Chromatid Exchanges



SOURCE: Biomedical Sciences Division, Lawrence Livermore National Laboratory.

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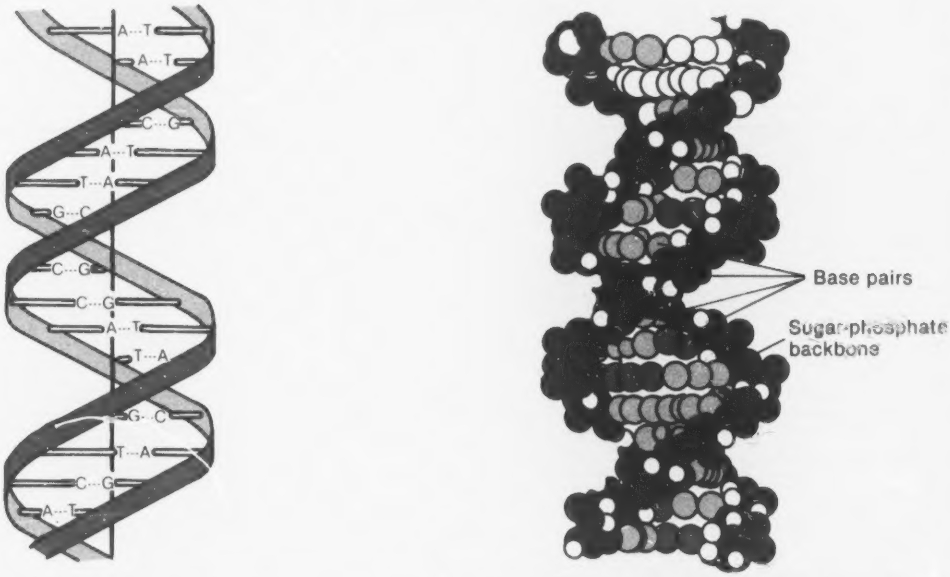
DNA, genes, and proteins

The genetic information contained within the familiar DNA double helix (fig. 5) is completely defined by the linear order of four chemical compounds known as nucleotide bases, adenine (A), guanine (G), cytosine (C), and thymine (T). These bases, attached to the double strands of the helix, interact in a specific fashion to form the rungs of the DNA ladder: A's can pair only with T's, and G's only with C's. Therefore, the two sides of the ladder are not identical but are "complementary." The chemical nature of the complementary base pairing is vital to the function of DNA. The pairing is specific, which ensures that the genetic information will be maintained, but not very strong, so that sections of the helix can "unzip" to expose the bases, thus making the genetic information available for use.

An ordered sequence of a few thousand nucleotide bases is the unit of heredity known as the gene. A gene has regulatory signals at either end specifying its beginning and end. The signals themselves are a series of nucleotide bases, usually on the order of 10 to 100 bases long. For the most part, one gene contains the information for the synthesis of one protein. Thus, the four bases, A, G, T, and C, depending on their order, contain the information for the synthesis of proteins. The genetic code is the same for all organisms. The difference between organisms, therefore, is not the inherent chemical nature of the genetic material, but the different sequences of nucleotide bases.

The DNA present in every cell of every living organism has the capacity to direct the functions of that cell. Gene expression is the way in which the genetic directions in any particular cell are decoded and processed into the final functioning product, usually a protein (fig. 6). In the first step,

Figure 5.—The Structure of DNA



A schematic diagram of the DNA double helix. A three-dimensional representation of the DNA double helix.

The DNA molecule is a double helix composed of two chains. The sugar-phosphate backbones twist around the outside, with the paired bases on the inside serving to hold the chains together.

SOURCE: Office of Technology Assessment.

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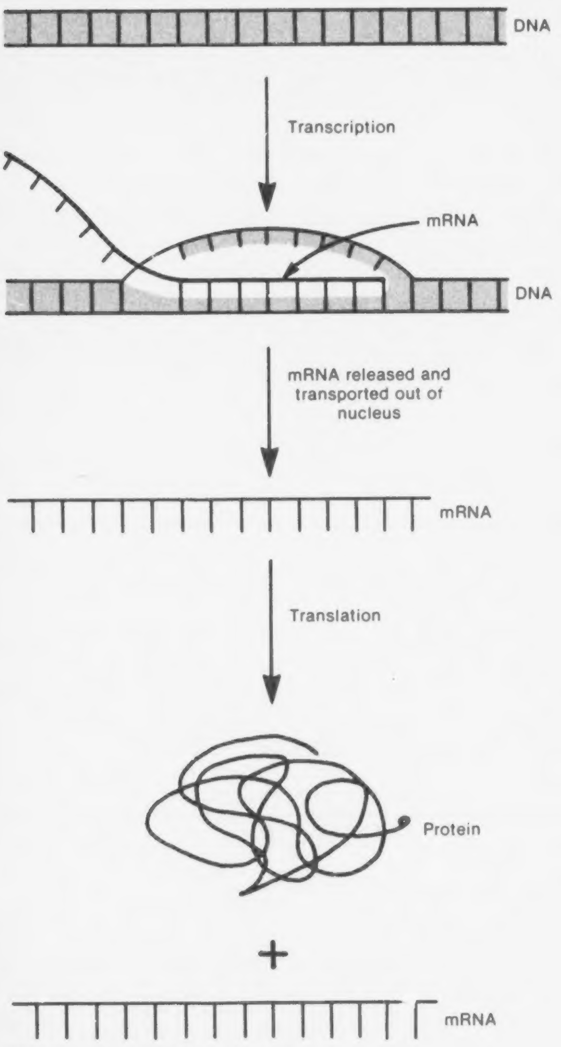
Figure 6.—Mechanism of Gene Expression



SOURCE: Office of Technology Assessment.

called transcription, the DNA double helix is locally unzipped, in the region of the gene of interest, and the intermediate product, messenger RNA (mRNA), a single-stranded, linear sequence of nucleotide bases chemically very similar to DNA, is synthesized. The transcription process dictates the synthesis of mRNA that is complementary to the section of unzipped DNA. The second step is translation. The mRNA, after release from the DNA, becomes associated with the protein-synthesizing machinery of the cell, and the sequence of nucleotide bases in the mRNA is decoded and translated into a protein. The protein goes on to perform its particular function, and when the protein is no longer needed, the protein and the mRNA coding for that protein are degraded. This mechanism allows a cell to "fine tune" the quantity of its proteins while keeping its DNA in a very stable and intact form.

Proteins actually perform the necessary functions of the cell. By far the most diverse group are the enzymes, or the proteins that catalyze all biological reactions. Another group, the structural proteins, are found, for instance, in cell membranes. Other proteins, such as hormones, have regulatory functions; still others have highly specialized functions—for example, hemoglobin carries oxygen from the lungs to the rest of the tissues.

Genetic variability in humans

Because all humans need to perform the same life-supporting tasks, they all have genes that code for the same types of proteins. But for any given protein, there may be many variants, some "normal" and some deleterious. This means that the genes that code for these variants are also slightly different. These forms of the same basic gene are called alleles. It is the variation in these alleles that forms the basis for diversity within species.

Variants have been discovered for many human genes. For example, of the 319 possible detectable variants of beta-globin, 104 had been observed by 1976. More than 80 different variants of glucose-6-phosphate-dehydrogenase (G-6-PD) have been identified, and some of these differ in their metabolic and clinical effects.

Although most variants are rare, a few occur with frequencies of at least 2 percent. The products of such variable alleles include beta-S globin (which produces a sickling of red blood cells), the A- G-6-PD allele, blood groups, and histocompatibility substances. One study estimated that for the "average" gene coding for an enzyme, approximately 6 percent of individuals will be easily detected as carrying a variant gene. Other variants, which are not so readily detectable, probably occur more frequently. Thus, it may be that for a given gene, 20 percent of the population might possess two variant alleles. If this is true, the prospects for detecting individuals with susceptibility-conferring genotypes by mass screening seem high.

At first glance, it would appear unlikely that genes conferring susceptibility to chemical or physical agents in the workplace could gain high frequency; they should have been selected against. This is not necessarily the case.

The frequency of an allele will decrease over the course of generations if the individuals who possess it have, as a result, lower reproductive fitness (that is, die before having children or have children who die before reproductive age). However, those who possess alleles whose only harmful effect results from workplace exposures may be well into the reproductive phase of their lives before their first exposure. If, in addition, a latent period occurs between exposure and harmful effect, as is the case for most cancers, those individuals may have completed their reproduction before the disease appears. Thus, the allele would not reduce reproductive fitness. Such alleles could attain high frequency by random genetic drift or by an advantage that they confer to the reproductively active members of the population or that they conferred in an earlier evolutionary setting. For example, the hemoglobin alleles (such as sickle cell) gained in frequency because of the protection they conferred against malaria.

On the other hand, in situations where the harmful effect of an allele only occasionally manifests itself during the reproductive phase, some individuals with that allele would have their reproductive years shortened. Therefore, the average reproductive fitness of those possessing the allele would be slightly less than those lacking it. Over many generations, even a small decrease in reproductive fitness would diminish the frequency of the allele and, in the absence of other effects, result in its eventual disappearance. Thus, there may not be very many alleles present today with high frequency whose harmful effects are usually manifested later in life.

Harmful reactions to newly invented chemicals also may occur frequently simply because most individuals lack genetically determined mechanisms for detoxifying them or repairing the damage they cause. It remains to be determined whether biological detoxification methods have already evolved for many chemicals that cause disability today. If they have not, only rare individuals may be able to cope with those chemicals. Thus, the susceptibility-conferring alleles then would be the predominant types.

Even when a genetically determined detoxification mechanism has evolved, it might protect against an acute effect of the chemical (and consequently confer a reproductive advantage), but the mechanism itself might cause a change in the chemical that increases the chance of a latent harmful effect. If the latency period exceeds the reproductive period, this long-term effect would not have a selective disadvantage.

Mutation

A mutation is a heritable change in the sequence of nucleotide bases.* A mutation can be an insertion or deletion of a base or a base change. A base change is usually caused by a mispairing reaction during DNA replication which effectively changes one base pair to the other one. For instance, if a modified A mispairs with a C, the C will correctly pair with a G during replication and will have effectively converted an A-T base pair to a G-C base pair in one of the daughter cells.

Mutations normally occur at a low rate and, indeed, are the raw material for the evolutionary process. They can occur in spaces between genes and thus be neutral, or they can occur within genes. Occasionally an intragene mutation will cause the gene to encode a protein that is better adapted to its function, but most mutations within genes are deleterious (1). Mutations within genes are well documented in humans. In fact, at least 1,000 human diseases are known to be genetic in origin (5), and many more are thought to have a significant genetic contribution.

Induced mutations can be caused by genotoxic (gene-damaging) chemicals or ionizing radiation. Mispairing of nucleotide bases during DNA replication can be caused by chemical modification of bases or by the incorporation of compounds that look like bases. Some compounds insert themselves between base pairs, distort the helix, and thus cause additions or deletions of nucleotide bases during DNA replication. Radiation is thought to cause mutations by damaging the structure of the nucleotide base or the backbone of the DNA helix.

DNA damage that can lead to mutations can often be repaired. A mismatched base pair or chemically modified base will distort the double helix and alert cellular repair mechanisms. The damaged section of the DNA strand can be excised and new DNA synthesized using the other strand as a template. It is important for DNA to be repaired prior to replication because mismatched bases become fixed during replication.

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*Some of the chromosomal aberrations discussed above are actually mutations, but for simplicity, the use of "mutation" in this report will refer to nucleotide base changes whereas "chromosomal aberration" will refer to gross structural changes visible in the light microscope.

Single gene traits

A genetic trait is any detectable condition that is known to be inherited. The easiest case to study genetically is a trait specified by a single gene. Examples include sickle cell anemia and Tay-Sachs disease. Suppose a hypothetical single gene trait B determines the normal condition and the rarely occurring allele b results in an observable deficiency. Because there are pairs of each chromosome, a normal individual will be either BB (both chromosomes of the pair have the B allele) or Bb (one chromosome has the B allele and the other has the b allele). An afflicted individual will be bb (both chromosomes of the pair have the b allele). When both chromosomes carry the same allele, the trait is homozygous (that is, BB or bb); when the two chromosomes carry different alleles, as in the Bb individual, the trait is heterozygous. In a heterozygous trait where only one allele appears to be contributing to the observable condition (in this case, B), that allele is said to be dominant. The allele (b) that is masked by the dominant allele is recessive. Only when both chromosomes of a pair carry the recessive allele will the deficiency be detected. A heterozygote for the trait is called a carrier.

The actual genetic constitution of a trait (or an individual) is the genotype. In the case of BB and bb individuals, the genotype is reflected in the observed trait, or phenotype. In general, a specific phenotype associated with the heterozygous genotype is not observed. In this simple case, because B is dominant, the phenotype of the heterozygote is the same as the homozygote (BB). In addition, the phenotype reflects the interaction of the genotype with the environment.

Occasionally, a heterozygous trait is expressed at an intermediate level, that is, neither allele is fully dominant or recessive. In these cases the alleles are said to be codominant, and the observed phenotypes reflect both homozygous and heterozygous genotypes.

The deficient phenotype (from genotype bb) may be expressed by various symptoms, but it is the result of a single protein deficiency. The result may be due, for example, to a nonfunctional structural protein, the lack of a protein or hormone, or a deficient metabolic enzyme. Moreover, there are many traits whose phenotypic expression is the result of several gene products working together. An example of a polygenic trait is a person's height.

Mutations, chromosomes, and cancer

Both mutations and chromosomal aberrations are thought to play a role in the set of diseases known as cancer. Many (about 90 percent) of the chemicals known to cause cancer (carcinogens) in animals are also known to cause mutations in in vitro tests (6). In fact, chemicals being tested for their potential carcinogenic effects are first screened for their ability to cause mutations. One theory of carcinogenesis postulates that one or more mutations causes a cell to reproduce out of control and, subsequently, form a tumor. Strongly supporting a mutational origin of many cancers is the fact that they arise from a single somatic cell; that is, the cancer genotype, once present, is stable and passed on to daughter cells during tumor growth.

Most cancer cells have abnormal karyotypes; there are frequently changes in chromosome number, and more recently, it has been shown that there are an unusually high number of chromosomal aberrations. It is not known whether these abnormalities are a cause or an effect of the malignant state, but several inherited diseases,* in which there is an increased aberration frequency, are associated with an increased risk for developing cancer (9). These single gene recessive diseases are thought to be due to deficiencies in DNA repair processes, and the chromosomes of afflicted individuals are much more susceptible to breakage caused by radiation and chemicals. Clearly, these chromosomal instabilities precede any malignancy, because these individuals also have many aberrant cells that are not malignant. Still, some types of cancer (for example, myelocytic leukemia) correlate with specific chromosomal abnormalities.

One hypothesis holds that mutations and/or chromosomal aberrations are precancerous events, but, as yet, there is very little definitive scientific evidence to support this. A recent report has shown that the gene presumably responsible for one type of human bladder cancer differs from its normal counterpart by a single base mutation (10).

A conspicuous feature of carcinogenesis is the generally long period of time that elapses between the initial exposure to the carcinogen and the appearance of the disease. Why this time course is so long is unknown, but based on extensive animal experimentation, carcinogenesis can be separated into two distinct steps, initiation and promotion. Evidence has accumulated to suggest that initiation may be nothing more than mutagenesis, the most powerful initiators being the most potent mutagens. However, initiation alone apparently is not enough to produce the disease; promotion is also necessary.* The nature of promotion is still obscure. Various agents or physical insults (for example, wounding) can act as promoters, often a long time after initiation. The feature all promoters have in common is that they provoke increased cell multiplication of initiated cells; generally, they do not affect noninitiated cells. How rapid cell proliferation in the presence of a mutation could lead to a malignant state is unknown. At any rate, both genetic and environmental factors can influence whether one develops cancer, but the elucidation of these factors has not yet been achieved (6).

---

*Bloom's syndrome, ataxia telangiectasia, Fanconi's anemia, and xeroderma pigmentosum.

If cancer indeed has one or more genetic components, individuals who have the "wrong" combinations of genes may be genetically more susceptible to cancer. Several gene products that could be involved in determining one's inherited predisposition to cancer are genes for DNA repair, immune function, and carcinogen metabolism.

Certain complex pathways of DNA repair are beginning to be understood in higher animals. If damaged DNA is repaired in such a way that the nucleotide base is the same as the old, no permanent change has taken place. On the other hand, if mistakes are made during DNA repair due to deficiencies in the repair enzymes, the new base sequence will be different from the original one, and, by definition, a mutation will now exist. Hence, this deficient repair may play an intimate role in the mechanism of formation of some kinds of mutations. Individuals who have deficient pathways of DNA repair might then be more susceptible to cancer.

Immune deficiencies, or the inability to fight disease, also might predispose one to cancer. If initiation is the result of a somatic cell mutation, then potential cancer cells would continually be formed in our bodies at a low frequency. An efficient immune system would recognize these cancer cells as "foreign" and kill them. Hence, reduced immune function may increase the risk for cancer. Indeed, many chemical carcinogens are also immunosuppressants, and this has been speculated to be part of their carcinogenic mechanism. Organ transplant patients who receive massive doses of immunosuppressants are at increased risk for developing cancer later (8).

Finally, genetic differences in the ability to metabolize chemical agents to carcinogens may be involved in determining an individual's predisposition to cancer. Many chemicals alone are not harmful, but in mammals a metabolic activation by complex enzymatic systems can occur to form an active carcinogenic compound. However, there are also enzyme systems that deactivate potential carcinogens by forming compounds that are safely eliminated from the body.

Hence, a person who is deficient in DNA repair or cellular immune function or who has higher levels of the activation enzymes or lower levels of the deactivation enzymes may be more susceptible to chemically induced cancer than someone who is competent in DNA repair or immune function or who does not activate specific chemicals to carcinogens very well or who efficiently eliminates potential carcinogens by deactivation. Because each of these critical functions may show a wide spectrum of activity, cancer susceptibility may be quite variable as well (2,4).

Body fluids used in genetic testing

The detection of genetic traits or abnormalities in humans presents special problems because tests for these factors must be noninvasive, that is, they must use easily obtainable material. Several sources of body fluids are available, but usually blood, urine, and feces have been used in genetic tests. Because they are waste material and do not participate in the normal functions of the body, urine and feces have limited application in genetic testing. Their current use is as sources of material for the detection of mutagens. The assumption is that the presence of mutagens in waste material indicates that those mutagens also were present in body tissues.

---

*Some agents, known as "complete carcinogens," can act as both initiators and promoters.

Only blood serves as an easily obtainable source of body fluid and cells for genetic tests, and, again, an assumption is made that blood reflects events happening in the other parts of the body. An argument against this assumption is the fact that chemicals act in tissue-specific manners. On the other hand, in experimental situations with animals, it has been found that blood cells do reflect exposure levels. In addition, because blood is so easy to obtain, much of the research on genetic mutations in humans has been done on blood proteins.

Blood can be divided into two components: cells and serum, the fluid in which they float. Serum can be assayed for three types of compounds: proteins normally found in serum such as clotting factors, protein degraders, and antibodies; proteins from liver cells, some of which are important in carcinogen metabolism; and mutagens.

The two types of blood cells, red and white, can be used to detect genetic traits or abnormalities. Red blood cells, or erythrocytes, have both enzymatic functions and an oxygen-carrying function, handled by the protein complex called hemoglobin. Because the red cells are so easily obtained, a great deal is known about both the normal and genetic variants of erythrocyte proteins. In addition, hemoglobin is probably the easiest protein in the body to isolate in large quantities. For these reasons, tests to identify genetic or chemical variants of hemoglobin have been used to detect the presence of mutagens and are included in this assessment.

White blood cells, or leukocytes, are a heterogeneous set of cells involved primarily in the immune functions. A subset of these cells, the lymphocytes, are the cells most often used to detect mutagenic activity. It is the lymphocytes that are assayed for chromosomal aberrations and SCEs. Many other biochemical tests to detect mutagenesis also use lymphocytes.

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Chapter 5

Principles of Genetic Testing

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Chapter 5

Principles of Genetic Testing

Genetic testing of employee populations is a basic method for identifying individuals or groups with particular inherited traits or evidence of genetic damage in certain cells who may be at increased risk for disease. It is the application of tests to a group of apparently well persons in order to identify those who have a high probability of developing a disease so that prevention or early treatment is possible. Genetic testing involves laboratory examination of body fluids such as blood to determine the presence of inherited traits or changes in chromosomes or deoxyribonucleic acid (DNA). It includes both genetic screening and genetic monitoring. Each uses specific laboratory tests but the goals of each are slightly different.

A genetic screening test is a one-time procedure used in occupational settings to identify individuals with certain inherited traits. Some scientists have hypothesized that these traits may cause the individual to be at increased risk for certain occupational diseases when exposed to hazardous chemicals (1). Because these inherited traits do not change, a single test for them is sufficient.

Genetic monitoring periodically examines induced genetic damage in certain cells of workers. Some scientists believe that certain types of genetic damage may indicate exposure to hazardous agents and may be associated with an increased risk for certain diseases, in particular cancer. The laboratory tests search for endpoints different from those used in genetic screening, and the procedures are applied initially to determine a baseline of genetic damage prior to exposure and then periodically to determine changes in that damage. Changes in certain genetic characteristics of the population may indicate that the population is at an increased risk for disease.

Before a rational decision can be made on the value of any genetic screening or monitoring program in the workplace, two questions must be answered. The first is: "Does the test being employed reliably identify either the genetic trait or type of damage in question?" The answer to this question requires an assessment of the particular laboratory techniques used to identify genetic traits or genetic damage from exposure to hazards. Only after achieving a positive answer to this question can the following question be asked: "Does this particular trait or damage cause the individual or population to be at increased risk for disease?" The answer to this question involves assessing the conclusions of epidemiologic studies regarding the association between these genetic factors and disease. Available scientific evidence indicates that the first question can be answered in some cases; the answer to the second one awaits significantly more research. In ascertaining whether the test identifies either a genetic trait or damage, the tests must be subjected to scientifically recognized analytical criteria: validity, reliability, predictive value, and relative risk (6).

Validity, reliability, and predictive value

The validity of genetic testing—i.e., the probability that a test will correctly classify true susceptible ("positive") and true nonsusceptible ("negative") individuals—should be evaluated before the test is placed into routine use. Few tests are 100 percent valid. The reasons are both methodological (i.e., the inherent variability in test performance) and biological (i.e., the influence of other genetic as well as environmental factors).

From the distribution of the test results in those for whom the presence or absence of a genetic endpoint (trait or genetic damage) has been confirmed, the validity of the test at different cutoff points can be determined (fig. 7). Two separate, independent characteristics are subsumed under validity; each depends on the cutoff point that is selected. These are:

- sensitivity, or true positive ratio—the frequency with which the test will be positive when the genotype in question is present; and
- specificity, or true negative ratio—the frequency with which the test will be negative when the genotype in question is absent. An ideal test would be 100 percent sensitive and 100 percent specific. In actual practice this does not occur.

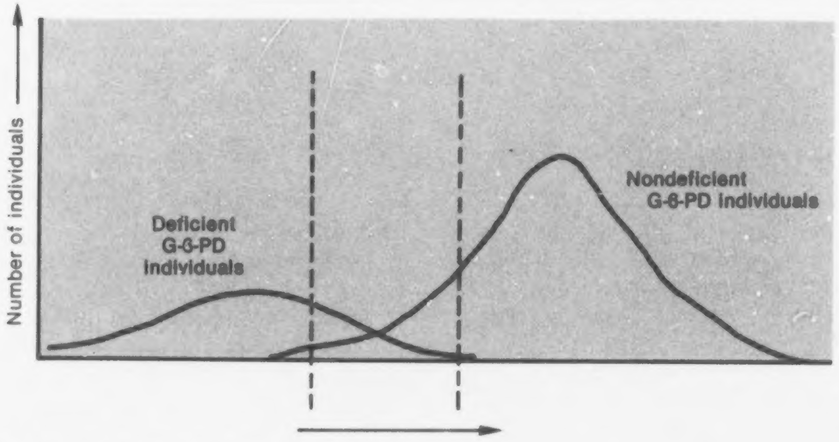
Sensitivity and specificity are usually inversely related. That is, one usually achieves high sensitivity at the expense of low specificity and vice versa. This can be demonstrated by examining a hypothetical situation to determine the cutoff point for a screening test (fig. 7).

The selection of the actual cutoff point depends on the objective of the screening or monitoring test. If the objective is to identify all individuals with the abnormal genotype or genetic damage, cutpoint A would be selected. As the figure shows, such a cutpoint will pick up all true positives, but it will also result in many false positives. If no followup test is planned in the routine operation of a screening program, this cutoff point would mislabel many people as affected who are not. With cutoff point B, no individuals would be falsely labeled as affected, but some affected individuals would be falsely labeled as unaffected. Methods of determining the cutpoint that minimize costs of mislabeling or that maximize the information to be gained from the screening tests are available (5,7).

In addition to validity, reliability under conditions of routine use must also be demonstrated. That is, tests of the same specimen must repeatedly give the same result whether performed by several different laboratories or by the same laboratory on several occasions.

Predictive value is related to sensitivity, specificity, and the prevalence of the trait or genetic damage in the population. When the prevalence of a particular trait or genetic damage is low in the population, even a highly specific test will give a relatively large number of false positives because many persons being tested will not have the endpoint. The likelihood that an individual with a positive test has the disease, and vice versa for a negative test result, is the predictive value of the test. The importance of prevalence for the predictive value of a test can be seen in the following example. Table 12 presents hypothetical data

Figure 7.—Example of a Hypothetical G-6-PD Distribution



SOURCE: Office of Technology Assessment.

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Table 12.—Calculation of Predictive Value[a]

	Number with positive test	Number with negative test	Total
Genotype present	990	10	1,000
Genotype absent	990	98,010	99,000
Totals	1,980	98,020	100,000

Predictive value of a positive test result $= \frac{990}{1,980} = 0.50$

Predictive value of a negative test result $= \frac{98,010}{98,020} = 0.9999$

[a] Sensitivity, specificity = 0.99.

SOURCE: N. A. Holtzman, "Principles of Screening Applied to Testing for Genetic Susceptibilities to Harm From Workplace Exposure," prepared for OTA, September 1982.

for calculating the predictive value of a positive test result for a genotype frequency of 1 percent (1,000/100,000) (2). Even where the sensitivity and specificity are arbitrarily set high, 0.99, the positive predictive value is only 50 percent. This means that the test correctly measures the result only half the time; in the case of genetic screening, half of the workers with positive test results would, in fact, not have the predisposing genotype. Followup testing would have to be a part of a screening or monitoring program in order to detect the false positives or false negatives.

Table 13 shows the influence of selected frequencies when a cutpoint for the screening test is used that yields both a specificity and a sensitivity of 0.99. The predictive value of the positive test will vary between 0 and 0.92 percent as the frequency of the genotype varies between 1 and 10,000 per 100,000 (0.001 to 10 percent) people screened. The chance that a person with a negative test result does not have the genotype is also shown. Note that all the predictive values for a negative test result in the table are very close to 1.0. A genotype frequency (prevalence) of approximately 50 percent (not shown) is needed before the predictive value of a negative test rises to 0.99 (3,6).

Table 13.—Influence of Genotype Frequency on the Predictive Value of Screening Tests[a]

	Frequency of the genotype (per 100,000)				
	1	10	100	1,000	10,000
Predictive value of a positive test result	0	0.01	0.09	0.50	0.92
Predictive value of a negative test result	1	1	1	1	1

[a] Sensitivity, specificity = 0.99.

SOURCE: N. A. Holtzman, "Principles of Screening Applied to Testing for Genetic Susceptibilities to Harm From Workplace Exposures," prepared for OTA, September 1982.

Relative risk

The proportion of workers likely to contract a disease depends not only on the previously mentioned variables (reliability, validity, frequency of the genotype), but on the relative risk for the disease imposed by the genetic trait or damage. Information for calculating relative risk* can be collected in two ways. In the prospective approach, all individuals comprising the population exposed to the agent would be tested for the genotype and followed for a set period of time to determine the incidence of harmful effects in those with the specific genotype and in those without it. Alternatively, a retrospective study could be used to compare the frequency of the genotype among workers who developed the harmful reaction to the frequency in workers who did not. (Note: The latter approach would yield a risk ratio which is a close approximation to the relative risk measure.)

---

*Relative risk is the ratio of the incidence of disease among exposed persons divided by the same rate among nonexposed persons.

Table 14 shows the influence of relative risk and genotype frequency on the proportion of workers at risk for harm from exposure discovered by a test whose sensitivity and specificity are set equal to 0.99 (3). For example, with a genotype frequency of 1,000/100,000 (1 percent), those with the genotype must be 100 times more likely to suffer adverse reactions before the screening test will discover half of those who will suffer harm. In addition, in this table and the two preceding tables, sensitivity and specificity levels have been set at 0.99 in order to elucidate the other components. In actual studies sensitivity and specificity are never as high. Thus, the ability to detect predisposing factors is further compromised.

Table 14.—Influence of Genotype Frequency and Relative Risk[a] on the Proportion of Workers at Risk for Harmful Reactions Who Will Have Positive Screening Test Results[b]

Frequency of genotype (per 100,000)	Relative risk 5	10	50	100
	Proportion of at-risk workers discovered by screening			
1	0.01	0.01	0.01	0.01
10	0.01	0.01	0.01	0.02
100	0.01	0.02	0.06	0.10
1,000	0.06	0.10	0.34	0.50
10,000	0.36	0.53	0.84	0.91

[a] $\text{Relative risk} = \frac{\text{incidence of adverse reaction in those with the susceptible genotype}}{\text{incidence of adverse reaction in those without the susceptible genotype}}$

[b] Sensitivity, specificity set at = 0.99

SOURCE: N. A. Holtzman, "Principles of Screening Applied to Testing for Genetic Susceptibilities to Harm From Workplace Exposures," prepared for OTA, September 1982.

From this discussion, it is clear that attention must be paid to validity, reliability, predictive value, and relative risk or screening and monitoring in the workplace may turn out to be costly and of little benefit. The less frequent the genetic endpoint being tested, the less likely that the person with a positive test result will truly have that trait or damage. Unless testing of high validity is restricted to conditions in which the frequency of the trait or damage is high, a significant number of false positives and false negatives can be expected. False positives increase the social, economic, and psychological costs of screening; false negatives reduce the health benefits. When the frequency of the endpoint is high, however, lowering exposure for the entire work force may be the most effective way of reducing disability. If a genetic screening program were instituted, a population that would ensure a relatively high frequency (greater than 1 percent) of the trait of interest should be chosen. One way to increase the frequency in a population is to select a subgroup that is expected to have a higher frequency of the trait than the general population. A monitoring program should be instituted only when bacterial and animal tests have proven that the chemical in question is mutagenic or carcinogenic. Moreover, worksite sampling should establish that the hazardous agent is present in areas where workers would be significantly exposed.

OTA's assessment of occupational studies

The correlation of a test endpoint (for example, chromosomal damage) with the later occurrence of disease is difficult to ascertain because the possibility remains that adverse consequences from exposure will not occur in all of those with the predisposing condition; other genetic or environmental factors (for example, smoking) may be necessary for the development of the disease or may contribute differently in different individuals. Because an illness may have multiple causes, it may also occur in workers without the predisposing condition. Thus, genetic tests may identify only a proportion of the workers who will develop adverse reactions.

Part III of this report contains OTA's assessment of relevant monitoring and screening studies conducted on human populations. The following criteria were applied to determine whether the studies were based on sound methodological approaches (4):

- Is the observed association consistent? That is, has the same association been observed in similar studies?
- Is the association specific? Was there a mix of exposure levels or grouping of individuals such that the precise nature of the effect of exposure is difficult to ascertain?
- Is the strength of the association strong? Is it strong enough to indicate a causal relationship between exposure and disease?
- Is there a dose-response relationship? Does it appear that higher exposure levels are associated with higher prevalences of the disease?
- Is there a biological mechanism to explain the association?
- Was the study designed so that the assumptions of statistical methodology were met? Has the sample been properly drawn?

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Part III

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Chapter 6

Genetic Monitoring in the Workplace

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Chapter 6

Genetic Monitoring in the Workplace

Although humans have been exposed to chemicals and radiation for thousands of generations, the numbers and amounts of these potentially hazardous agents in the environment have increased dramatically since the industrial revolution. Moreover, certain occupational groups are exposed to these substances over many years at much higher concentrations than is the general population.

While the contribution of toxic chemicals and ionizing radiation to the human genetic burden has not been directly shown, some of these agents do cause mutations and chromosomal damage in laboratory animals. Geneticists are concerned that exposures to new mutagenic agents could increase the number of gene mutations in the human population and hence the incidence of disease. Because of the increasing chances for exposure to harmful agents, it is desirable to develop tests that identify the mutagenic and clastogenic (chromosome-damaging) potential of chemicals and ionizing radiation. When hazards are identified, prevention programs can be considered that will reduce exposures to the hazards. In addition, genetic tests may be useful to monitor human populations for exposure.

Ideally, an occupational monitoring technique would provide early, reliable, and quantitative information regarding "biologically significant" exposure* to hazardous agents. Once a biologically significant level of exposure has been established, intervention measures to eliminate or significantly reduce worker exposure and prevent untoward biological effects could be implemented.

Genetic monitoring in the workplace involves the periodic testing of employees to assess damage to their deoxyribonucleic acid (DNA) or chromosomes from exposure to hazardous agents. Currently, genetic monitoring techniques are most useful for identifying or monitoring exposure to a chemical that causes genetic damage. The objective of these techniques ultimately is to predict risk of disease due to genetic damage.

There are two types of techniques covered in this assessment. The first type, cytogenetic techniques, looks for gross changes in chromosomal structure. These techniques, including tests for chromosomal aberrations and sister chromatid exchange (SCE), represent the currently used methods for monitoring for genetic damage. Other monitoring techniques that also look for damage to the genetic material have been proposed for human populations. These newer noncytogenetic techniques may offer advantages in sensitivity, cost, and performance time over the cytogenetic methods, often because of automation, but most of them have had little actual application in human monitoring programs at the present time. This chapter reviews the occupational studies done to date, first examining the use of cytogenetic monitoring and then noncytogenetic monitoring.

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*The definition of "biologically significant" exposure is a difficult one, and there is by no means a concurrence of opinion among health care professionals. It normally refers to an exposure level that can cause detectable damage or disease.

Cytogenetic monitoring

The empirical association between chromosomal damage and mutagenic/carcinogenic agents established from animal studies implies that chemically induced chromosomal aberrations and SCEs may be used as possible biological dosimeters (measures of exposure) for human exposure to these agents. There are three natural extensions of this dosimeter hypothesis. One is the idea that studies using cytogenetic endpoints* may be used to identify human carcinogens or mutagens.** The second is that these studies might identify populations at risk for cancer and other diseases as a result of exposure to these clastogens. Last, the studies may identify individuals in those populations who, because of a defect in DNA repair mechanisms, may be particularly predisposed to chromosomal damage. In the workplace, the goals of such studies would be to determine acceptably safe levels for occupational exposure to chemicals and radiation (that is, those levels associated with minimal, or acceptable, risk of disease) for the average population and to insulate susceptible individuals from the chemical.

This section examines the appropriateness of chromosomal endpoints to detect occupational exposures to chemicals and radiation. This critical review of the literature seeks to determine whether chromosomal endpoints can be used as a measure of occupational exposures and whether the results of cytogenetic monitoring are a predictor of risk for disease for either groups or individuals. The discussion is limited to studies that are pertinent to adult somatic effects resulting from occupational exposures.

Associations between chromosomal aberrations and disease

Many diseases are thought to involve somatic cell genetic defects. Interference with immune function, manifested as autoimmune disease, allergy, or increased susceptibility to infectious agents, may involve somatic cell genetic changes. Hence, induced chromosomal aberrations may prove to be related to these clinical states. However, there are no studies, either in animals or in man, that address the possible association between induced chromosomal aberrations or SCEs and immune function.

Photo credit: National Institutes of Health

Cytogenetics involves the examination of chromosomes under a microscope

Other diseases of the blood/lymph system, such as aplastic anemia and multiple myeloma, also may be the result of somatic cell genetic changes. Because cytogenetic monitoring usually utilizes blood lymphocytes as the chromosomal source, cytogenetics may prove useful in predicting whether individuals exposed to high levels of clastogens may be candidates for these blood cell diseases, but this association is only speculative.

Cancer is the disease most commonly hypothesized to be associated with induced chromosomal aberrations, undoubtedly because of the large animal literature linking carcinogens with chromosomal aberrations. Additionally, many types of human cancer cells contain specific chromosomal aberrations (31,34,63,76,93,99,141). Chromosomal aberrations have been found for both lymphoproliferative disorders, such as leukemia, and solid tumors. The strength of the association between the specific aberration and the presence of cancer varies from one cancer to another. At one extreme, the Philadelphia chromosome (a translocation from the long arm of chromosome #22 most often to the long arm terminus of chromosome #9) correlates highly with chronic myelogenous leukemia, with 85 to 95 percent of patients having this marker chromosome in their affected cells. On the other hand, in the case of a pair of identical twins, each carrying the specific deletion associated with Wilms tumor, only one of the twins developed the disease (76). Thus, even when specific chromosomal markers are involved, other nongenetic factors can play a role in the development of cancer.

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*The term endpoint refers to the biological response to exposure being monitored. In this section, two endpoints are discussed, chromosomal aberrations and SCEs.

**Studies would not be done primarily to investigate this issue, but results identifying human carcinogens or mutagens could derive from cytogenetic studies investigating risk for disease. The identification of mutagens and carcinogens is done with animals and extrapolated to humans; cytogenetic studies would either verify the animal data or refute the extrapolation.

Correlation between chromosomal aberrations, SCEs, and carcinogenicity

The extensive literature on animal studies that use chromosomal endpoints has recently been appraised and reviewed by the U.S. Environmental Protection Agency's (EPA) Gene-Tox Program committees (80,113). The Gene-Tox committee for mammalian in vivo and in vitro cytogenetic assays (chromosomal aberrations) reviewed 177 papers published through October 1978 using several somatic cell systems (113). For one or another of these systems, 150 chemicals were reviewed.

According to the Gene-Tox findings for chromosomal aberrations and SCEs, the data base for chemicals that have been adequately studied in animal or in in vitro systems is quite limited, and the number of the chemicals for which carcinogenicity is known is even more limited. In addition, the carcinogenicity data were generated in separate studies from the chromosomal data and are not directly comparable. But within these restrictions, it would appear that the induction of chromosomal aberrations and SCEs by chemical agents are reasonable indicators of carcinogenicity, with the former possibly being the better predictor. However, for both endpoints, examples exist of chemicals that cause chromosomal damage but not cancer, and vice versa. In order to relate genotoxicity more closely to humans, the Gene-Tox review recommended human cells as being suitable for in vitro studies. The review is still is progress, and EPA has yet to issue any recommendations on the predictive value of any of the techniques.

A recent review by Gebhart (57) summarizes the world's literature concerning the agreement between chromosomal aberrations and SCEs. Gebhart found a 30 percent disagreement between these two endpoints where the same chemical had been evaluated for aberrations and SCEs both in vitro and in vivo. This indicates that the fundamental way in which a particular chemical interacts with the DNA to produce SCEs may be different from the mechanism that produces chromosomal aberrations.

Chromosomal studies on groups

This section provides a comprehensive review of occupational studies using chromosomal endpoints. Many of the studies fall short of ideal. For instance, confounding factors, such as cigarette smoking, were not always determined, and some studies examined populations too small to produce reliable results. In general, more recent studies are better designed and executed. However, rather than discard the evidence of the older studies, the strengths and weaknesses of all the studies are reviewed, and overall conclusions are drawn.

The review covers studies addressing the normal range of values for chromosomal endpoints, studies on the chromosomal endpoints and health status of atomic bomb survivors exposed to ionizing radiation, and occupational studies on the chromosomal endpoints of workers exposed to ionizing radiation and specific chemicals.

For the occupational studies, the following questions were asked:

- Was there substantial evidence of an increase in the endpoint that could be associated with exposure to a specific agent? Was there a dose response? Were chronic as well as acute exposures monitored?
- Was there evidence to link any of these endpoints with increased risk for disease?
- Are these tests sufficiently sensitive to permit detection of effects at current occupational exposures?

- For each of the agents discussed in detail, is there evidence that cytogenetic endpoints can detect susceptible individuals?

STUDIES ON UNEXPOSED POPULATIONS

Several large studies have examined the range of chromosomal aberration and SCE frequencies and the variables affecting them in unexposed populations (13,15,28,29,35,59,71,79,86,88,90, 95,100). Seasonal variations, age, sex, smoking, and alcohol effects have been reported, although not consistently for every study. From these studies, it is apparent that background frequencies for chromosomal aberrations and SCEs may fluctuate greatly. The background frequencies reported in several studies are shown in appendix D for chromosomal aberrations and in appendix E for SCEs. Comparison of findings from studies with varied laboratory methodology is difficult but useful to the extent that it conveys a sense of possible variability for these endpoints.

The range of reported frequencies per cell for individual aberrations found was:

- chromatid breaks: 0.11 to 6.72 percent,
- chromosome breaks: 0.1 to 3.0 percent,
- exchange aberrations: 0 to 0.34 percent,
- cells containing any aberration: 0.2 to 8.5 percent, and
- SCEs: 5.8 to 16.2 per cell.

These wide variations suggest that the range of "normal" values for chromosomal endpoints may be dependent on the particular laboratory methodology. Certainly the fortyfold differences seen for background values of chromosomal aberrations are much greater than those reported in individual studies between occupationally exposed and unexposed groups.

STUDIES ON ATOMIC BOMB SURVIVORS

Since the end of World War II, the Japanese survivors of the atomic bombs and their offspring have been extensively monitored by the Atomic Bomb Casualty Commission, recently redesignated the Radiation Effects Research Foundation, for residual and latent biological effects. These studies have been a joint effort between eminent Japanese and American scientists and are ongoing (102). Refinements are still being made in dosimetry estimates and epidemiology.

This Japanese population has been observed to have an increased risk for many types of cancer (14). Leukemias were the first evident cancers, with incidence peaking 7 to 8 years after exposure. The incidence of all leukemias for this population has subsided with time, but it is not clear if the risk for leukemias has declined to background values.

With the decline of leukemias, the onset of other types of cancer has become apparent. To date there is a clearly increased risk for cancers of the thyroid, female breast, and lung. Excess stomach and salivary gland cancers are suspected but not yet confirmed. In contrast to the leukemias, the time of onset for breast cancer in exposed populations has not been earlier than would be predicted on the basis of studies in unexposed populations. Rather, breast cancer has appeared at a higher, dose-related frequency at the age when it usually occurs. All of these cancers have shown a dose dependence for radiation, but the shape of the dose-response curves differs with different cancers. These differences in patterns of cancer incidence are consistent with the widely held opinion that the mechanisms of radiation-induced cancers are complex and perhaps different from one cancer to another.

In conjunction with these morbidity and mortality studies, extensive cytogenetic investigations on these survivors have revealed a dose-dependent increase in chromosomal aberrations (14). These cytogenetic studies have been possible because some of the chromosomal abnormalities induced by ionizing radiation are very long lived. The frequencies of these aberrations seen in the atomic bomb survivors are very high compared to the aberration frequencies found in occupational exposures, even in individuals receiving small doses (less than 1 rad*). The reason for this is unknown.

The ongoing epidemiological studies on these same individuals provide an unparalleled opportunity to examine directly the relationship between chromosomal aberrations and cancer. In an extensive study reported by King, et al. (75), where chromosomal aberrations, malignancy, and other clinical findings were tracked for individuals in the Hiroshima population, the tentative conclusion was that such correlations do not exist.

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*A rad is a measure of absorbed dose of ionizing radiation.

With populations or groups, however, the studies on the Japanese clearly demonstrate a relationship between estimated radiation dose and certain cancers and between radiation dose and chromosomal aberrations. But for individuals, elevated frequencies of chromosomal aberrations are not reliable predictors for risk of cancer or other somatic cell diseases. Thus, even these extensive studies do not provide evidence that radiation-induced chromosomal aberrations mean that individuals with these aberrations will necessarily develop cancer.

Several points should be borne in mind in relating these studies to the ionizing radiation studies discussed below. First, the Japanese studies reported quite high frequencies for rare aberrations, even in groups receiving less than 1 rad. Second, because of the manner in which the studies were designed, little or no cytogenetic information is available on the group receiving exposures between 1 and 100 rads. This group is probably the most comparable, in terms of equivalent genotoxic dose, to groups receiving occupational exposures to radiation. Thus, because of the different types of chromosomal aberrations involved and, because of probably larger radiation doses in the exposed Japanese populations, it is difficult to relate the significance of these findings to occupational studies. Finally, the Japanese studies deal with the effects of a single, large, acute dose of radiation. In the majority of occupational situations, the effects of chronic lower doses of radiation may not be so easily detected.

OCCUPATIONAL STUDIES ON IONIZING RADIATION

If chromosomal aberrations induced by radiation are indicative of some health risks, albeit for a group, then occupational cytogenetic studies on workers exposed to chronic lower doses of radiation may be of some value in setting acceptable standards for occupational exposure to radiation. Several occupational studies have been done on uranium miners, workers in a plutonium processing facility, and nuclear powerplant workers (17,20,21,22,23,46,89,98). Every study reviewed has shown that increases in chromosomal aberrations are associated with occupational exposures to ionizing radiation. If these aberrations are as stable as those in the Japanese, they would not necessarily indicate recent exposures under current occupational exposure standards, but rather accumulated exposure over several years.

From these studies, it is not clear if the chromosomal aberration endpoint is sensitive enough to detect chronic exposures within the current occupational exposure standard of 5 rems* per year. Occupational groups would have to be studied at low-level chronic exposures to determine if individuals exposed to the current occupational standard have increased frequencies of aberrations.

OCCUPATIONAL STUDIES ON ARSENIC

Arsenic is a ubiquitous element that can occur in several chemical forms, some of which have commercial uses as fungicides, insecticides, and herbicides. It also has been used for medicinal purposes, for instance, in the treatment of ailments ranging from asthma to psoriasis and syphilis. When arsenic is eaten or inhaled, about 50 percent of the dose is absorbed. Of the absorbed dose, roughly half is excreted within 2 days. The remainder is eliminated more slowly, and a fraction can accumulate in the body, where it is distributed in many different tissues (85). Arsenic is classified as a human carcinogen (72). Several types of cancers have been associated with occupational exposure to arsenic in smelters, in the chemical industry, and in gold mining (103).

Both chromosomal aberrations and SCEs have been reported to be elevated in individuals exposed to arsenic, with SCEs possibly being the more sensitive indicator (26,97,110). Chromosomal effects of arsenic exposure are long lived and possibly reflect cumulative exposure. It is not clear if chromosomal endpoints can detect low-level chronic exposure to arsenic, because the exposures in the studies reviewed here were relatively high. The one study on arsenic in an occupational setting (97) is not sufficient to permit a decision on the suitability of cytogenetic endpoints for measuring exposure.

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*A rem is a rad multiplied by a number that takes into account the potential damage-causing ability of a particular type of ionizing radiation in a biological system.

OCCUPATIONAL STUDIES ON BENZENE

Benzene is a constituent of fossil fuels and also is a major industrial and laboratory chemical. As a result, a substantial number of people are chronically exposed to benzene at work, and many more receive transient exposures outside the workplace, for instance, while pumping gasoline. As with arsenic, benzene is classified as a human carcinogen (72), with an excess of leukemias, particularly erythroleukemia, associated with high exposures (73,134). Benzene is also a potent blood cell poison, with manifestations including pancytopenia (reduction of all blood elements) and aplastic anemia. The current occupational exposure standard for benzene in the United States is 10 parts per million (ppm), a time-weighted average for 8 hours.

Benzene is one of the most widely studied chemicals in occupational cytogenetics. Several studies consistently have shown that exposure to high doses of benzene (greater than 40 ppm) is associated with chromosomal aberrations, even though frequencies are low in comparison with radiation-induced effects (52,53,54,111,112,131, 132,136). The aberrations appear to be stable for years and most likely reflect cumulative rather than recent exposure. Whether exposure to benzene within the current occupational standard of 10 ppm induces chromosomal aberrations has yet to be determined.

OCCUPATIONAL STUDIES ON EPICHLOROHYDRIN

Epichlorohydrin is a highly reactive major industrial chemical that has been extensively studied for genotoxic activity (126). It is mutagenic in micro-organisms, causes chromosomal aberrations in mouse bone marrow, and induces chromosomal aberrations in human lymphocytes in vitro (126). Epichlorohydrin causes nasal tumors in rats by the inhalation route at levels higher than 10 ppm (N. Nelson, unpublished study). One study has indicated a slight, but not statistically significant, excess in respiratory cancers among workers exposed to this chemical (45), and IARC (72) found that it "could not be classified as to . . . carcinogenicity for humans."

The only adequate cytogenetic study on epichlorohydrin (127) showed that occupational exposure to the chemical may be associated with low frequencies of chromosomal aberrations. No studies have been done linking chromosomal aberrations with risk for disease in a population exposed to epichlorohydrin.

OCCUPATIONAL STUDIES OF ETHYLENE OXIDE

Ethylene oxide is an extremely reactive chemical whose commercial uses are primarily as a sterilizer of medical products and as a chemical intermediate. Ethylene oxide has been shown to cause leukemias in rats by the inhalation route at doses higher than 33 ppm (58). It can induce chromosomal aberrations in vitro and mutations in tester micro-organisms (46). Because of ethylene oxide's volatility, there is a high potential for occupational exposure in situations where it is not properly contained. The current Occupational Safety and Health Administration's (OSHA) occupational exposure standard is 50 ppm, time-weighted average. Two reports (57,68) suggest an increase in leukemia among workers exposed to this chemical.

Three published studies associate present levels of ethylene oxide found in the workplace with chromosomal aberrations and possibly SCEs (56,109,130). However, frequencies for these endpoints were low. Two additional studies on ethylene oxide (S. Galloway and A. Carrano, personal communication) are now being conducted. Preliminary reports on a study being conducted at three Johnson & Johnson plants indicate a consistent dose-response for both chromosomal aberration and SCE endpoints. Statistically significant increases in cytogenetic aberrations were seen even in a plant where exposures range from 1 to 10 ppm. No effects were found at less than 1 ppm (32, 101).

OCCUPATIONAL STUDIES ON LEAD, CADMIUM, AND ZINC

Lead, cadmium, and zinc tend to occur together in mineral deposits in nature and, therefore, in occupational exposures. High exposures to lead or cadmium can produce both acute symptoms of poisoning and chronic effects. Lead poisoning involves nerve degeneration, interference with some metabolic processes, and, in its severest form, mental retardation. Lead acetate is carcinogenic in rats, but has been negative for chromosomal aberrations and SCEs in vitro (80,113). Cadmium has been shown to cause birth defects and cancer in rodents, and there is some evidence for human carcinogenicity (72). Occupational exposure to cadmium has been associated at least tentatively with lung and prostate cancers (36). Both cadmium and lead tend to accumulate in the body with chronic exposure, a point which may be important in interpreting the occupational studies on these agents because damage may reflect a cumulative exposure.

Zinc, unlike lead and cadmium, is necessary for the function of some of the enzymes involved in DNA replication and repair, and it is possible that cadmium and lead, when present in high amounts, can replace zinc in these enzymes. If this happened, the enzymatic activity would be greatly reduced.

WARNING
LEAD WORK AREA
POISON

Photo credit: Occupational Safety and Health Administration

Cytogenetic monitoring has been explored as a possible technique for monitoring worker exposure to lead

Many conflicting findings exist in the literature addressing occupational exposure to lead, cadmium, and zinc (16,25,37,38,39,50,51,69,89,104, 105,120,132). Increased frequencies of chromosomal aberrations and correlations with blood lead values have been reported often enough to provide some credibility to the correlations, but many good studies have failed to find such relationships. Perhaps one reason for such discrepancies is the diversity of occupational exposures studied. Different work situations could have entailed quite different kinds of exposures with respect to the specific compounds in the work environment and possibly to different primary routes of exposure. The relationship between the three elements and chromosomal aberrations clearly is complex and awaits further elucidation.

OCCUPATIONAL STUDIES ON VINYL CHLORIDE MONOMER

Vinyl chloride monomer is a major industrial chemical used to make polyvinyl chloride plastics. It is mutagenic for tester micro-organisms and causes chromosomal aberrations in rats treated with 1,500 ppm by the inhalation route, a very high level (7). Vinyl chloride is a human carcinogen (72) and has been implicated in several types of cancer (103).

Elevation of chromosomal aberrations to relatively high levels by occupational exposure to vinyl chloride is consistent and well documented (5,8,41,49,55,62,74,77,114,118,129). The chromosomal aberration endpoint seems to be more sensitive than the SCE endpoint to vinyl chloride exposure. In contrast to the aberrations seen with benzene, arsenic, and ionizing radiation, the aberrations associated with vinyl chloride exposure are short lived, disappearing over days or weeks. The mechanism for this difference is unknown. Chromosomal aberrations, in this case, could be used to document recent exposure but not necessarily cumulative exposure. Elevations in chromosomal aberration frequencies have not been detected when documented exposures have been less than 5 ppm. (The OSHA standard states that the vinyl chloride level shall not exceed 1 ppm during any 15-minute period). Thus, chromosomal aberrations and SCEs do not seem to be sensitive enough to detect chronic low-level exposures to vinyl chloride for the number of cells usually scored (200 or fewer) per individual.

Conclusions

Elevated chromosomal endpoints are associated with occupational exposures to ionizing radiation and may be associated with exposure to some chemicals (arsenic, benzene, and vinyl chloride), particularly where long-lived aberrations (arsenic and benzene) are involved. The nature and longevity of the aberrations vary from one agent to another. For some chemicals such as benzene, the aberrations may persist for years. In these instances, the aberrations would indicate a cumulative exposure. For others, such as vinyl chloride monomer, the aberrations disappear quickly after reduction of exposure, and the cytogenetic tests could monitor exposure only over short time periods. It is not known whether cytogenetic monitoring will detect chronic low-level exposure. Hence, the appropriateness of chromosomal endpoints for occupational monitoring needs to be determined on a case-by-case basis for each chemical. In addition, a monitoring program should only be instituted when bacterial and animal tests have proved that the chemical in question is mutagenic or carcinogenic.

No occupational studies directly relate positive findings for any chromosomal endpoint with increased risk for any disease. Therefore, the clinical significance of a positive occupational cytogenetic study is unknown; nor is it known whether cytogenetic monitoring can be used to determine "safe" levels of exposure.

Retrospective cytogenetic studies done in conjunction with morbidity and mortality studies on populations of survivors of the atomic bomb attacks in Japan have found both high frequencies of stable chromosomal aberrations, particularly complex aberrations, and increased risk of cancer. On the other hand, there is no known correlation between an individual's chromosomal aberrations and his or her risk for cancer.

Cytogenetic monitoring, or any other test based on a single endpoint, may never be sufficient to predict health risks for an individual (with the possible exception of the Philadelphia chromosome), because the causes of cancer and other chronic diseases are complex and multifactorial, with some genetic and some environmental components. As more is understood about the molecular basis of each disease, an appropriate battery of tests may be designed with a variety of endpoints, each reflecting some aspect of the potential causes. Given the present information, any single endpoint, such as chromosomal aberrations or SCEs, may have some predictive value for a group. Even findings about groups with increased chromosomal damage require epidemiological studies on the populations to determine if increased risk for disease accompany the damage.

More research is needed to identify any relationships between chromosomal aberrations, SCEs, and disease in populations. At the present time, genetic monitoring may be most useful for detecting exposure to harmful agents. The most pressing questions yet to be answered concerning the use of monitoring in the workplace are: What is the biological significance of small elevations of aberrations or SCEs? Is there consistency between a given frequency of aberrations or SCEs induced by different agents and risk for disease?

Priorities for future research

Additional occupational cytogenetics studies are needed, combined with epidemiological investigations, to define further the meaning of induced chromosomal aberrations and SCEs. There is also a need to develop faster and easier tests for occupational genetic monitoring. Discussions with scientists involved in this work led to the following suggestions for future research:

- There is a need to standardize the laboratory conditions for cytogenetic tests.
- The best method of categorizing chromosomal damage for analysis has not been determined. Perhaps more comprehensive and critical analysis of results already available could contribute to the understanding of

both the effects of confounding variables and the biological mechanisms involved in the induction of chromosomal aberrations and SCEs. It may be worthwhile to single out the percentage of cells with large numbers of SCEs and to display the chromosomal aberrations of each category for each individual in a study, including a distinction between the percentage of cells with aberrations and the percentage of aberrations per cell.

- New cytogenetic tests that are less labor intensive and that possibly could be automated are essential if cytogenetic testing is to be conducted on a large scale. Manual scoring, such as is done now, is so labor intensive and time-consuming that most cytogenetics laboratories in the United States are now working at capacity. Test scorers require several years of training to reach the point of consistent scoring. The use of a fluorescent-activated cell sorter has been studied as a possible means of automating chromosomal analysis, but this technique has intrinsic insensitivities and has not successfully been used to detect low frequencies of aberrations in human chromosomes (107,140).
- Further research needs to be done on in vitro sensitivity of human lymphocytes to chemicals encountered in the workplace. This approach could eventually have some value in predicting human clastogens as well as individual sensitivities to clastogens.
- The variables influencing baseline (normal) frequencies of chromosomal aberrations and SCEs need to be elucidated.
- There apparently has not been a prospective study done that looks for the association between chromosomal aberrations and risk for somatic disease in the same individual. There is a critical need for such studies, where individuals with no previous occupational radiation or chemical exposure are tracked, with concurrent comparisons. The National Institute for Occupational Safety and Health has developed protocols for studies on radiation-exposed workers, but has yet to begin them. Any study addressing biological effects of current occupational exposure standards for radiation or chemicals should examine some individuals whose entire occupational history has been under the current standards.

Noncytogenetic monitoring

Because of the need for inexpensive and rapid tests to monitor human exposure to mutagens, many tests originally developed to screen chemicals for mutagenic activity have been modified to identify human exposure to mutagens.* All of these tests, either directly or indirectly, identify the presence of mutagens or DNA damage resulting from the presence of mutagens. Most of these developments are recent and, for the most part, have not been used for routine human monitoring.

Survey of monitoring methods

Virtually none of the tests described in table 15 has as yet been established as a reliable technique for monitoring human populations. The only test applied to population monitoring on more than a single trial basis has been the analysis of urine for mutagens. A few of the remaining tests have been used in human pilot studies, but these studies were for baseline analysis and not actual monitoring.

MUTAGENS IN BODY FLUIDS

The assumption is made that the presence of mutagens in body fluids represents a genetic hazard. Mutagenic activity in these fluids can be shown by using the rapid screening tests developed for bacterial or in vitro cell culture systems.

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*The extensive literature on animal studies using noncytogenetic endpoints for mutagenicity or carcinogenecity has recently been reviewed and evaluated by EPA's Gene-Tox program (61). Most of the papers have yet to be published, but two reviews have been published on specific mutation analysis in Chinese hamster cells (1970). Both of these papers state that the correlation between mutagenicity in this type of assay and animal carcinogenicity is high.

Table 15.—Summary of Noncytogenetic Monitoring Techniques

Test type	Description
Mutagens in body fluids:	
1. Urine	Body fluids used as test materials in bacterial or in vitro cell culture mutagenicity assays.
2. Feces	
3. Blood	
Somatic cell damage:	
1. Binding of mutagens to hemoglobin	Alkylation of the hemoglobin protein
2. Specific mutation analysis in lymphocytes	Technique that measures gene mutatation
3. Unscheduled DNA synthesis in lymphocytes	Technique that measures DNA damage
4. Hemoglobin gene mutations	Immunological technique that measures gene mutation
5. Chemically damaged DNA bases	Technique that measures DNA damage
6. Lymphocyte transformation	Technique that probably measures gene mutation
Germ cell (sperm) damage:	
1. YFF test	Detection of abnormal number of chromosomes
2. LDH-X variants	Immunological technique that measures gene mutation

SOURCE: Office of Technology Assessment.

Since blood and urine are routinely collected in medical examinations, these types of tests could be integrated into a medical monitoring program.

A number of studies have been performed with body fluids, primarily urine, from humans presumably exposed to mutagens in their occupation or exposed to mutagens in the course of medical treatments (82,83,123,124). Lifestyle factors such as cigarette smoking also have been studied (2, 133,139). It is anticipated that urine analysis increasingly will be used for human epidemiological studies, both because it successfully identifies mutagens and because this test probably can be automated. Less commonly used tests of fecal sources and blood are not expected to be useful in general screening because of inherent technical problems.

Analysis of urine for the presence of mutagens.—The use of urine collected from humans as a test material is readily applicable to human monitoring situations for the following reasons (18):

- Studies have demonstrated that mutagenic activity can be detected in the urine of individuals exposed to various therapeutic drugs and industrial chemicals and of individuals with specific lifestyles or occupational experiences.
- Collection of urine samples is easy and can be obtained from both males and females on a regular schedule.
- Both mutagenic and chemical analysis can be performed simultaneously from a single collection of urine.
- Urine samples can be tested for the presence of mutagens not only in bacterial cells but also in mammalian cells.
- The costs and performance time associated with this approach are amenable to large-scale sampling studies.

There are also drawbacks to the use of this test in occupational settings. For example, only recent exposures can be measured. Moreover, the presence of mutagens in urine has not been translated into a known risk to the individual. Presence of mutagens in the urine can be considered evidence of exposure to a mutagenic chemical or to a chemical that forms mutagenic metabolites which are eventually excreted. However, excretion of mutagens may be a protective process. In fact, the absence of mutagens in the urine could be interpreted as evidence that the mutagens are bound to cellular molecules (thus potentially causing damage) and are not available for urinary excretion. Consequently, knowledge of the metabolic fate of the suspected mutagens is critical to the proper interpretation of this monitoring technique. Moreover, there may be many confound-

Photo credit: National Institutes of Health

Noncytogenetic monitoring involves the use of biochemical tests

ing variables in urine analysis. For instance, the urine of cigarette smokers has been shown to contain mutagens (139).

Analysis of feces for the presence of mutagens.—Because cancer of the colon is a major cause of cancer mortality in Western countries, the incidence of the disease has been associated with diet (12,96,103). Examination of human feces for mutagens is gaining some attention following a report (24) that showed that feces from individuals on typical Western diets contain high levels of mutagens. Consequently, analysis of human fecal samples might represent a monitoring approach for examining the relationship of dietary factors to specific types of cancer. Because of technical difficulties, such as concentration of the feces, the use of this procedure in occupational settings currently is limited.

Analysis of blood serum for the presence of mutagens.—There are only two reports on blood serum analysis for mutagenicity (40,82). Because of the difficulty of obtaining large quantitites of serum, it is doubtful that serum analysis will contribute to the array of human monitoring techniques unless the detection tests could be made more sensitive.

SOMATIC CELL DAMAGE

Binding of mutagens to hemoglobin.—The possibilities for using hemoglobin from red blood cells as a biological dosimeter have been explored by Ehrenberg and coworkers in a series of experiments on mice using alkylating agents (43, 106,121). The assay is designed to measure alkylated amino acids in hemoglobin from exposed individuals. This phenomenon is not a genetic alteration, but protein alkylation strongly implies concurrent alkylation of DNA, a presumed first step in the production of mutations. The assay seems to work well for several alkylating agents. It can be used as a dosimeter, that is, it gives a positive dose-response curve, and it is a measure of accumulated damage over a period of a few months. This latter point is important because many other tests have to be done within a day or two of exposure.

The accumulation of alkylated groups in hemoglobin and the relatively large amounts of hemoglobin that can be isolated from one blood sample and analyzed, together with the availability of sensitive chemical and analytical techniques, make it feasible to determine small quantities of alkylated amino acids formed as a consequence of exposure to mutagens in the environment. For the most part, however, the procedures have been used only for mice injected with known mutagens. In the single report on the practical application of these procedures to human monitoring, Ehrenburg (42) showed that hemoglobin molecules were alkylated in workers exposed to ethylene oxide.

Before these techniques can be used in routine monitoring, more extensive validation studies are needed to standardize protocols, evaluate reproducibility, and determine intrinsic individual variability. Once these factors are established, the procedure might have wide applications for specific chemical classes.

Specific mutation analysis in lymphocytes.—The production of the enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT) in humans is controlled by the hpt gene located on the X-chromosome (65). Cultured cells in which hpt has mutated are easily detected because of their resistance to normally poisonous guanine analogs, such as 6-thioguanine (TG). Thus, cells lacking HGRPT can be selected and grown by exposing them to one of these analogs in the culture medium. The frequency of TG-resistant (presumed mutant) cells in the peripheral blood lymphocytes of normal persons is very low (128), but the frequency increases among cancer patients being treated with known mutagens (4,128). Although the technique has been hampered by high background levels, recent modifications appear to have resolved some of these problems (3).

Although no studies have been undertaken, it is speculated that the detection of TG-resistant cells that arise in vivo could play a role in occupational monitoring. This technique could provide a sensitive assay for the induction of genetic mutations in human somatic cells. An increase in the percentage of TG-resistant cells in individuals exposed to toxic agents in the workplace might indicate exposure to a mutagen.

Unscheduled DNA synthesis in lymphocytes.—The damage to DNA by chemicals or radiation is often repaired by cellular mechanisms that remove the damaged area and replace it with new nucleotides (33,116). A test that measures this DNA repair, referred to as unscheduled DNA synthesis (UDS), has been suggested as a good indicator of exposure of chromosomes to mutagenic agents since the amount of DNA repair induced should be proportional to the amount of DNA damaged. In fact, reported data with human lymphocytes suggest that UDS is associated with mutation and chromosomal aberrations (108).

This assay also can be used to identify agents that inhibit DNA repair. Chemicals capable of inducing DNA damage while simultaneously inhibiting DNA repair may be especially hazardous. Results of a preliminary study of workers exposed to ethylene oxide show increases in both chromosomal aberrations and suppression of DNA repair synthesis (109).

There have been few UDS studies on lymphocytes in vivo. Limited studies of normal human lymphocytes (108) and lymphocytes from exposed humans (109) indicate that sex, age, and blood pressure may affect both background and chemically induced levels of UDS.

At present it appears that this assay can best be used to study the nature of tissue specificity of chemical DNA damage. For instance, compounds that cause stomach cancer may induce UDS in stomach tissue but not in liver tissue. On the other hand, it may not be a very good assay for mutagenesis because it is a measure of DNA repair, not damage, and repair may not correlate with genotoxicity.

Hemoglobin gene mutations.—Hemoglobin proteins can be altered by single gene mutations, and specific antibodies prepared against altered hemoglobin proteins can be used to detect these rare variants. Normal individuals generate the rare variants at a rate of about one variant per 10 million red blood cells. If the specific antibodies are linked to a fluorescent molecule, an automated, fluorescent-activated cell sorter can detect these rare cells with high sensitivity and specificity (92). Presumably, individuals exposed to mutagens would have an increased rate of production of the variants. This method could provide an excellent tool for evaluating human populations since it can be conducted objectively, quantitatively, and economically. Some preliminary pilot studies, using blood samples from individuals on cancer chemotherapy drugs or radiation therapy, found that the frequencies of abnormal hemoglobin were within the normal range but statistically higher than the frequencies for the corresponding controls (Omenn, personal communication).

Detection of chemically damaged DNA bases.—The detection of chemically damaged DNA bases is a direct measure of binding of a chemical to DNA. This binding can interfere with accurate DNA base pairing, thus causing mutations during DNA replication. Several detection methods have been described recently (1,64,66,138). All these methods are extremely sensitive and some, depending on the chemical, can detect as few as one event per cell. This level is in the range necessary for a test to be predictive for chronic low-level exposure.

There are limitations to the study of chemically damaged bases. It is a measure of an early event and a base change may not result in a mutation. For instance, the mutated bases could be repaired prior to cellular DNA synthesis and be of no consequence at all. It also is not known how persistent the damaged bases are. For instance, in monitoring a population, it is necessary to know when to collect samples and then whether the damaged bases found are a result of recent or prior exposure.

The detection of damaged DNA bases has moved beyond the laboratory. A prospective epidemiological study was begun recently on coke oven workers; the researchers are using specific antibodies to detect benzo(a)pyrene bound to DNA bases (137).

Lymphocyte transformation assay.—Several reports (30,60,117) suggest that mammalian cells exposed to mutagenic chemicals in vitro exhibit an enhanced susceptibility to transformation, a condition that has many similarities to tumor cells. It is possible that a modification of this transformation assay could be used to monitor exposure to harmful chemicals. The lymphocytes from exposed individuals are grown in culture under conditions that select for transformation. Presumably, increased exposure will yield more transformed cells.

GERM CELL DAMAGE

Studies on germ cells have focused exclusively on sperm. The advantage of monitoring sperm, aside from the ease of obtaining viable cells, is that studies using sperm have tested about 10 times the number of chemicals that have been tested using any other cell type. Whether toxicological studies of sperm will reflect the genetic status of somatic cells is unknown, but, assuming that they will, two assays show promise in an occupational setting.

YFF test.—The YFF test purports to identify an extra Y chromosome. Sperm with increased fluorescence under a microscope in the presence of quiniline dye are scored as having more than one Y chromosome. They are abnormal and presumably arise due to abnormal chromosome segregation during cell division. Yet it has not been shown conclusively that the increased fluorescence is not due to a change in the fluorescence pattern of the other chromosomes. Thus, this change may be an important indicator of exposure to chemicals, but cannot be taken as a result of abnormal segregation. This sperm assay, because of its relative experimental ease, might be most useful in determining priorities for longer term studies of chemical agents.

LDH-X variants.—The principle on which this assay is based is the same as that of the test for mutant hemoglobin. Lactate dehydrogenase-X (LDH-X) is a protein found on the tail of sperm and is detectable by specific antibodies (27). Experiments with rats and mice have shown that LDH-X mutants are detectable with different antibodies (10,11). Presumably, LDH-X variants could be detected with a battery of different monospecific antibodies. One experiment with mice showed a linear relationship between increased dose of mutagen and increased mutant LDH-X molecules (9).

The presence of LDH-X mutants presumably will reveal whether an individual is sensitive to an environmental mutagen in an analogous fashion to the hemoglobin gene mutation assay. As in that assay, the method could be automated by using fluorescent-labeled antibodies and a fluorescent-activated cell sorter. The human LDH-X mutants need much better characterization, however, before this assay will find applicability in a routine monitoring situation (H. Malling, personal communication).

Conclusions

At present, there is not enough research experience using humans for most noncytogenetic techniques to determine accurately their usefulness in workplace monitoring situations. The detection of mutagens in urine is the only assay that has been used with human subjects often enough to show that spurious results will not be generated. The other techniques will require considerably more development to be considered of value as monitoring techniques. The most obvious deficiency in these tests is the lack of the availability of the normal baseline response. Without a good estimate of the range of responses in unexposed humans, the data from test populations will be difficult to interpret. Table 16 summarizes all of the human studies that used noncytogenetic methods.

Priorities for future research

Several of the noncytogenetic techniques may have potential for use in human monitoring. The characteristics necessary for a good workplace monitoring technique include the ability to detect accurately low levels of the abnormality being assayed, the likely prospects for automation, and low cost. Six of the tests discussed in this section potentially have these necessary characteristics, and their development could lead to better workplace monitoring. These tests include the detection of:

- mutagens in urine,
- alkylated hemoglobin,
- a specific mutation (HGPRT) in lymphocytes,
- hemoglobin mutations,
- chemically damaged DNA bases, and
- LDH-X variants in sperm.

Table 16.—A Summary of Noncytogenetic Methods Used in Human Monitoring

Technique	Population monitored	Reference
1. Mutagens in body fluids		
A. Urine	Rubber industry workers	Falck, et al. (47)
	Coke plant workers (smokers v. nonsmokers)	Moeller and Dybing (94)
	Nurses administering cytostatic drugs	Falck, et al. (48)
	Chemical workers in ink and solvent plants	Mazzoli (91)
	Patients receiving cancer therapeutic drugs	Siebert and Simon (123,124) Legator, et al. (82,83,84) Speck, et al. (125) Wang, et al. (135) Roxe, et al. (119)
	Patients receiving drugs	Legator, et al. (81)
	Cigarette smokers v. nonsmokers	Yamasaki and Ames (139)
B. Blood	Persons dosed with an antiparasitic drug which has mutagenic and carcinogenic activity	Legator, et al. (82) Dobias (40)
C. Fecal	Comparison of humans with different diets and geographical origin	Ehrich, et al. (44) Reddy, et al. (115) Kunhlein, et al. (78)
2. Somatic cell damage		
A. Hemoglobin alkylation	Workers exposed to ethylene oxide	Ehrenberg (42)
B. Specific mutations in lymphocytes	Cancer patients treated with chemotherapeutic drugs	Strauss and Albertini (128) Albertini and Allen (4)
C. Unscheduled DNA synthesis	Factory workers exposed to ethylene oxide	Pero, et al. (109)
D. Hemoglobin gene mutations	Cancer patients treated with chemotherapeutic drugs	Mendelsohn, et al. (92)
E. Chemically damaged DNA bases	Coke oven workers exposed to benzo(a)pyrene	Weinstein and Perera (137)

SOURCE: Office of Technology Assessment.

Chapter 6 references

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Chapter 7

Genetic Screening for Heritable Traits

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Chapter 7

Genetic Screening for Heritable Traits

Individuals differ widely in their susceptibility to environmentally induced diseases. Differential susceptibility is known to be affected by developmental and aging processes, genetic characteristics, nutritional status, and the presence of preexisting diseases (11,12). This chapter assesses the way in which genetic factors contribute to the occurrence of differential susceptibility to toxic substances.

Clearly, genetic factors do not act in isolation from physiological processes. Genetic influences may be exaggerated or diminished by one's age, diet, or overall health status. For example, while people with an erythrocyte glucose-6-phosphate dehydrogenase (G-6-PD) deficiency may be at increased risk to a variety of drugs, it is also likely that their nutritional status may be able to mitigate or enhance their susceptibility (23). Many disease processes are affected by multiple factors, any one of which may not explain the variation in responses within a population.

It has long been suspected that biological factors affect the occurrence of occupational diseases. In fact, during World War I, it was speculated that TNT-induced adverse effects were intensified by inadequate diets (9,10). In 1938, J.B.S. Haldane (42) suggested a possible role for genetic constitution in the occurrence of bronchitis among potters and even raised the possibility of eliminating the genetically predisposed person from potential unhealthy work environments.

This assessment of the evidence that selected genetic conditions affect the occurrence of occupational disease focuses on those few single gene traits where substantial data are available. For each genetic trait, the following questions were asked:

- What is its prevalence in the population?
- Is it compatible with a normal lifestyle?
- With what diseases does the trait correlate?
- In what industrial settings might the traits cause a person to be at increased risk?
- Is there an increased risk for homozygous or heterozygous individuals, or both?
- What do epidemiological studies show, and are they well designed?
- What is the cost, ease, and predictive value of the available tests for detection of the trait? (See app. F.)

This chapter also briefly discusses those traits for which there is limited evidence suggesting an association with occupational disease. The traits discussed here represent only a fraction of a percent of all human traits. The discussion does not intend to imply that these traits are necessarily responsible for most of the occupational diseases that could result from genetic predisposition. In fact, the traits discussed here most likely comprise very few of the potential predisposing traits when increased susceptibility to chemicals or ionizing radiation is the issue.

Many data on differential susceptibility to chemicals come not from industrial settings but from documented responses to prescription drugs. These studies are relevant in that the detoxification or activation pathways for drugs may operate on a wide variety of other chemicals. Where relevant, drug studies have been included in the analysis because it is possible that an extrapolation from a clinical to an industrial setting can be made.

Red blood cell traits

Because human red blood cells (erythrocytes) are so accessible, the genetic traits expressed in these cells are among the best characterized of all traits. Erythrocytes contain hemoglobin, the protein responsible for carrying oxygen to tissues and carbon dioxide away from them. Any reduction in this ability, caused by either nonfunctional hemoglobin or fewer erythrocytes, results in the clinical manifestation of anemia.

The prevalence of hereditary blood conditions varies greatly among different ethnic groups, with their highest occurrence being in tropical climates. It appears that several of these traits have been evolutionarily selected over time because they provide a partial resistance to malaria. Since most of these traits in their heterozygous form are compatible with a normal lifestyle, they give a selective advantage to people in areas where malaria is common. However, such heterozygous individuals may exhibit a greater sensitivity to toxic chemicals in an industrial setting.

Glucose-6-phosphate dehydrogenase deficiency and hemolytic anemia

G-6-PD deficiency is a sex-linked genetic condition, the G-6-PD gene being located on the X chromosome.* The gene's normal function is important for maintenance of erythrocyte membrane integrity. Under hemolytic (destruction of red blood cell membrane) stress conditions (as in the presence of oxidizing agents including some antimalarial drugs), the erythocyte membranes of G-6-PD deficient individuals break down and those persons develop anemia. Otherwise, these individuals are healthy.

For industry, the first suggestions that G-6-PD deficiency may be involved in worker susceptibility to chemically induced anemia occurred during the early 1960's (8,52,127). In addition, in 1963, Stokinger and Mountain (117) proposed a list of 37 industrial chemicals known to cause hemolysis to which those with a G-6-PD deficiency may be at enhanced risk. They further suggested that screening tests to identify G-6-PD deficient individuals be conducted as part of preemployment medical examinations in order to identify those individuals before job placement. Later, Stokinger and Mountain (116) reported that more than 15 industries, research centers, or health-oriented groups either were using the G-6-PD test or had inquired into its use. More specifically, they noted that industries most interested in the test were manufacturers of dyes and dye-stuff intermediates, metals (especially lead), and drugs.

In addition to medical and industrial oxidizing agents as potential causes of hemolytic anemia in G-6-PD deficient individuals, interest recently has focused on the effects of copper and ozone on G-6-PD deficient erythrocytes. Because erythrocytes of the Dorset sheep are G-6-PD deficient and also are quite susceptible to copper-induced hemolysis, it was speculated that G-6-PD deficient humans likewise may display an enhanced susceptibility to copper. Subsequent studies have supported this hypothesis (9,13). An hypothesis that G-6-PD deficient individuals may be at enhanced risk to ozone toxicity has recently been supported by in vitro experiments showing that G-6-PD deficient erythrocytes are more susceptible to oxidant damage than normal erythrocytes (14).

Numerous surveys of G-6-PD deficiency, employing different methods of identification, have been conducted among various groups of people in different geographical locations (4). The frequency of this trait is very high among U.S. black males (13 to 16 percent). Other population frequencies of this trait are: Caucasians: American, 0.1 percent, British 0.1 percent, Greek, 2 to 32 percent, Scandinavians, 1 to 8 percent, East Indians, 0.3 percent, Mediterranean Jews, 11 percent, European Jews, 1 percent; Mongolian: Chinese, 2 to 5 percent, Filipinos, 12 to 13 percent. There are many genetic variants of the G-6-PD allele. Of particular importance here is the Mediterranean variant in which G-6-PD activity ranges from 1 to 8 percent of normal, compared to the A − variant of American blacks which maintains 15 to 25 percent of normal G-6-PD activity. The greater severity of the enzyme deficiency is of clinical concern because individuals with the Mediterranean variant are likely to be considerably more susceptible to oxidizing agents and infectious agents (for example, hepatitis) and experience more serious hemolytic crises (4).

Many substances commonly used in industry are known to cause hemolytic changes, and it has been speculated that they present an increased risk to G-6-PD deficient individuals. A few of these substances have been evaluated in vitro and found to display a greater stress on G-6-PD deficient cells. However, the only specific industrial substances for which proof exists that G-6-PD deficient individuals are at greater hemolytic risk than normal individuals are certain aromatic amino and nitro compounds (for example, naphthalene, TNT, and naladixic acid) (4,80). No quantitative risk assessments of the hemolytic actions of these substances on those individuals have been published. What is emerging is a growing body of in vitro evidence strongly implicating the enhanced susceptibility of G-6- PD deficient erythrocytes to a wide variety of industrial and environmental oxidants. Such in vitro exposures have not been related to actual exposures.

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*The deficiency is found mostly in men because of their single copy of the gene. Women can be heterozygous carriers and not exhibit the deficiency. Women homozygous for the deficiency are known, but rare.

Sickle-cell trait and sickle-cell anemia

These genetic conditions result from the presence of an abnormal hemoglobin molecule, hemoglobin S (HbS) in the erythrocytes of affected individuals. HbS differs from the normal hemoglobin A (HbA) only by the substitution of an amino acid at a single location in the hemoglobin protein beta-chain.* The decreased solubility of HbS under conditions of low oxygen may result in the formation of a gel within red blood cells, distorting them and causing the cells to look like sickles under the light microscope. An individual with sickle-cell anemia is homozygous for HbS while one with sickle-cell trait is heterozygous for HbS. The homozygous person has 100 percent HbS while the heterozygous person has from 20 to 40 percent HbS; the latter will experience sickling only when blood oxygen is greatly reduced (22,115).

While those with sickle-cell anemia are known to have a reduced lifespan, the health hazards of sickle-cell trait are considered minimal or nonexistent under most circumstances (91). Some situations have been thought to cause sickling problems in those with sickle cell trait. For instance, four deaths were attributed to sickle cell trait in Army recruits in basic training at a high altitude (55). The Air Force until recently had a policy that excluded blacks with sickle cell trait from the Air Force Academy and flight training (124). However, it has been determined that not enough data are available to support that policy. The overwhelming majority of people with sickle cell trait in the United States apparently never have any problems associated with this genetic condition.

The gene for HbS is found at high frequency in equatorial Africa, parts of India, countries of the Middle East, and areas around the Mediterranean. Sickle cell trait is found in about 8 percent of U.S. blacks. The frequency of sickle-cell anemia is about 0.2 to 0.5 percent among American blacks. However, because this disease most likely would have revealed itself in overt illness prior to adulthood, preemployment physical testing would not be used to discover the condition (22).

According to a survey of major industries (see ch. 3), the majority of genetic screening done in the workplace has been for sickle cell trait. The purpose of this testing is not known.

The thalassemias and erythroblastic anemia

Thalassemia is an erythroblastic anemia, a deficiency in the production of red blood cells, occurring early in life and varying in severity from mild to fatal. The severe form, found in the homozygous state, is called thalassemia major; the milder condition, found in the heterozygous state, is called thalassemia minor. The classic Mediterranean form of thalessemia, the beta form, is thought to be caused by a deficiency in beta-chain production of hemoglobin A. A different form of thalessemia, alpha thalessemia, involves a disruption in alpha-chain synthesis. The homozygous state for the alpha condition is fatal, leading to intrauterine death (76).

Of particular concern to this report is the health status of both alpha and beta thalessemic heterozygous individuals because of the milder manifestations of the disease and their considerably greater prevalence in the population compared to homozygous people. The frequency of alpha thalassemia heterozygous individuals among American blacks is thought to range between 2 and 7 percent (85,126). In more limited surveys, those of Greek ancestry were reported to have a 2 percent incidence of heterozygous alpha thalassemia (98). Beta thalassemia heterozygous individuals comprise about 4 to 5 percent of Italian-Americans (93) and Greek-Americans (98). The health status of heterozygous individuals is difficult to generalize since there appears to be extremely broad differential expression of the clinical features of the disease. However, what does seem predictable is that symptoms of the disease, however mild, may be exacerbated when additional stress is encountered, for example, in the presence of bronchopneumonia or during pregnancy. In a thalassemia heterozygous individual, auxiliary mechanisms of blood production already have been called into action and, under stress, may no longer be able to handle the expanded activity needed to maintain normal hemoglobin levels (76).

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*The hemoglobin molecule is composed of four protein chains, two identical beta chains and two identical alpha chains.

Since persons heterozygous for the thalassemic trait have a compromised adaptive capacity to maintain blood production, it has been suggested that they may be at increased risk from hazardous chemicals. The research to date, mostly in Europe, has involved a limited clinical assessment of occupational exposures to benzene and lead on persons heterozygous for beta thalassemia (33,37,40,99,106,107). In light of the limited number of individuals studied and the lack of environmental monitoring, it is not possible to conclude that susceptibility to benzene and lead toxicity is enhanced in persons with thalassemia trait. However, the clinical studies suggest the need for epidemiologic investigations to test this hypothesis.

NADH dehydrogenase deficiency and methemoglobinemia

The transportation of oxygen to tissues is contingent on the capability of hemoglobin to bind oxygen reversibly, a process that relies on the iron atom in the protein. The binding of oxygen by hemoglobin involves the oxidation of the iron atom. When the oxygen is released, the iron atom typically returns to its reduced state. Occasionally it stays oxidized, thereby leaving the hemoglobin in an oxidized state called methemoglobin. Normally, only about 1 percent of total hemoglobin is present in this state because the capacity of the red blood cell to reduce this state is several hundred times greater than the spontaneous rate of oxidation. Methemoglobin levels accumulate when the rate of oxidation of the iron atom exceeds the reducing capacity; a change in the protein chain stabilizes methemoglobin, making it resistant to reduction; or there is a marked deficiency in the reducing ability of the red blood cell. The most important metabolic pathway for the reduction of methemoglobin involves an enzyme called NADH dehydrogenase, which accounts for about 60 percent of the normal reduction rate (110).

Methemoglobinemia in humans initially was reported in homozygous people who were exposed to certain drugs capable of increasing the rate of oxidation of the iron atom of hemoglobin, but persistently high levels of methemoglobin have been clinically diagnosed with no known exposure to chemicals that oxidize hemoglobin (62). Subsequent research on such individuals has frequently revealed an NADH dehydrogenase deficiency as the cause of the high methemoglobin levels (110).

A very high occurrence of hereditary NADH dehydrogenase deficiency has been reported among Alaskan Eskimos and Indians (112), Navajo Indians (2), and Puerto Ricans (47,111). Heterozygous carriers of this enzyme deficiency display about 50 percent of the normal enzyme activity, with the frequency of such carriers in the U.S. population thought to be about 1 percent (94,125).

Methemoglobinemia acquired from industrial exposures to various chemicals, especially aromatic nitro and amino compounds, ranges from mild to severe. With 10 to 30 percent methemoglobin, only cyanosis (bluish skin) is observed. At 35 to 40 percent, headaches and shortness of breath on exertion are reported. At 60 percent, lethargy occurs, and above 70 percent, deaths have been reported. Biological monitoring for exposures to cyanogenic aromatic chemicals at Du Pont's Chamber Works facility by measurement of methemoglobin levels and recording of cyanosis was carried out beginning in the 1940's (80). During the 10-year period following 1956, 187 episodes of cyanosis were detected, occurring in 143 employees. (These workers would be an appropriate group for clinical testings of NADH dehydrogenase activity.) The company regularly used results of the biological monitoring of work crews to pinpoint areas requiring tighter control of exposures (80). In possibly analogous cases of cyanosis in Viet Nam where American military personnel were given malaria prophylaxis, Cohen, et al. (19) did show that the affected men were partially deficient heterozygotes for NADH dehydrogenase.

It has been shown repeatedly that persons homozygous or heterozygous for NADH dehydrogenase deficiency display an increased risk of cyanosis following exposure to drugs that form methemoglobin. However, there have been no reports of industrial exposures indicating that those with NADH dehydrogenase deficiency are at increased risk to methemoglobin-forming agents, probably because industrial screening for such a condition has not been conducted.

Traits correlated with lung disease

Serum alpha$_1$ antitrypsin deficiency and susceptibility to emphysema

Homozygous serum alpha$_1$ antitrypsin (SAT) deficiency is an important biological factor predisposing the occurrence of emphysema (26,66,71, 78,103,105). In fact, it is recognized that nearly 80 percent of those with this genetic condition develop the disease. Since only 1 individual in 4,000 to 8,000 displays the homozygous trait, there has been little concern about the screening for such individuals. On the other hand, heterozygous carriers who display an intermediate SAT deficiency (about 50 percent of normal values) may be at increased risk of developing emphysema, especially if they smoke tobacco or work in dusty environments. Heterozygous individuals comprise about 3 percent of the U.S. population, or about 7 million persons.

Initial studies of SAT deficiency and its role in the occurrence of emphysema focused on the risk to the homozygous genotype. However, subsequent reports began to mention that the heterozygous carrier also displayed a significantly enhanced risk of developing emphysema, although at a much lower frequency than the homozygous individual (67,79). In general, much of the data supporting the notion that the heterozygote is at enhanced risk came from studies in the United States, Germany, and Scandinavia. These studies covered about 1,400 patients with emphysema, 6.2 percent of whom were heterozygous for SAT deficiency (3,66,88,89,114,121). That percentage is highly significant when compared with the expected prevalence of about 3 percent for this group. Other research methodologies also have supported these observations (27,70).

Despite a consistent trend in most research findings showing enhanced susceptibility of the heterozygous individuals to obstructive lung damage, several reports have not supported that hypothesis (16,20,72,84,90). For the most part, these dissenting reports have found no difference in pulmonary function between SAT heterozygous persons and controls matched for age and sex, and little, if any, increased risk of emphysema when smoking was brought into the analysis. Because about 90 percent of individuals with the heterozygous genotype will not develop symptomatic disease, some researchers feel those studies have not given the hypothesis of enhanced heterozygote risk an adequate evaluation.

Environmental factors play a dominant role in the etiology of emphysema. For example, studies have indicated that cigarette smoke has been found to significantly lower SAT activity in rats after three puffs (51), while investigations with normal individuals likewise have found that chronic smokers displayed a nearly twofold decrease in functional activity of SAT as compared to nonsmokers (30). Other experimental studies have suggested that cadmium (17,18) and ambient ozone at levels approaching the current OSHA standard of 0.1 ppm (time-weighted average over an 8-hour day) may be contributing factors in the development of emphysema because of their ability to inhibit SAT activity (54).

Emphysema is a multicausal disease (58,87) and the heterozygous state, by itself, is not a major predisposing factor in its development. It is possible, however, that in combination with other predisposing factors, some of which have been identified (1,31,69,77), the heterozygous individual could be at an increased risk. It is necessary to evaluate the relative contribution of these variables in the development of emphysema. If the associations prove to be valid and are amenable to widespread screening, such screening most likely would involve an assessment of several factors.

Aryl hydrocarbon hydroxylase inducibility and susceptibility to lung cancer

The differential ability to induce the enzyme aryl hydrocarbon hydroxylase (AHH) has been correlated with lung cancer. This enzyme, found in most mammalian tissues, is known to catalyze the first step in the metabolism of polycyclic aromatic hydrocarbons (PAHs), many of which are found in cigarette smoke and the industrial workplace. Being an inducible enzyme (one whose activity can be increased in the presence of certain compounds), AHH displays increased activity following administration of a number of agents such as PAHs, various drugs, steroids, and insecticides (21). AHH is thought to play a key role in the modification of PAHs into biologically active compounds by metabolizing them to epoxides which can bind to DNA and other macromolecules (39). Epoxide binding appears to be an initial cause of malignant transformation in cells. Consequently, PAH metabolism via AHH can result in activation to more highly mutagenic and carcinogenic intermediates.

There is considerable variation in the extent to which AHH can be induced in cultured leukocytes from different individuals. The induction has been reported to be under genetic control (59), with the normal Caucasian population divided into three distinct groups with low, intermediate, and high degrees of inducibility, all of which are compatible with a normal lifestyle (60). This variation was hypothesized to result from a single gene with the three groups representing the homozygous low and high alleles and the intermediate heterozygote. The phenotypic frequencies were calculated to be 53 percent for low inducers, 37 percent for heterozygotes, and 10 percent for high inducers.

Since the inducibility of AHH was found to be under genetic control and exhibited wide variation in the population, Kellermann, et al. (60), sought to evaluate whether AHH inducibility could help to explain differential susceptibility to lung cancer presumably caused by PAHs which may have been activated to carcinogenic compounds. The lung cancer patients studied displayed a marked shift from the normal phenotypic frequencies in that only 4 percent were low inducers, 66 percent were moderate, and 30 percent were high. The authors concluded that the risk of lung cancer for the groups with intermediate and high inducibility was 16 and 36 times greater, respectively, than that of the low inducibility group.

A variety of research teams have sought to replicate and extend these findings because of their public health implications. Four studies have supported the initial findings (41,53,102,123). For the most part, these studies have shown that persons with lung and laryngeal cancer displayed significantly greater lymphocyte AHH inducibility than controls. With some exceptions these studies were better designed than the original Kellermann, et al. (60), report, but they did not investigate the genetics. Not all reports, however, even support the association between AHH inducibility and susceptibility to lung cancer (95,96).

A methodological issue that may lead to difficulties in reproducing the work of others is the seasonal variation in AHH levels; this variation implies that measurements of AHH activity cannot be collected in a population over prolonged periods of time. Also, the lymphocyte AHH inducibility assay is difficult to standardize (65). A significant improvement in the cell culture procedure or another way of measuring the genetic trait is essential before large-scale population studies can be undertaken.

A genetic basis affecting susceptibility to environmentally induced lung cancer has been documented overwhelmingly in animal studies (92) and supported by human epidemiologic investigations (122). However, the identification of a precise and reliable marker or predictor of risk to lung cancer—such as AHH inducibility—is currently unresolved.

The theory of Kellerman and associates that susceptibility to PAH-induced lung cancer is in part a function of the ability to induce AHH remains to be unequivocally established, but is still of public health interest. To date, the total number of cancer patients studied in the testing of this hypothesis is less than 1,000. Given that in 1981 the number of deaths from lung cancer in the United States alone was estimated to be more than 105,000, there is a need to evaluate this hypothesis once a valid and reliable test has been developed.

Other characterized genetic traits

Acetylation and susceptibility to arylamine-induced bladder cancer

Acetylation in the liver is a common pathway for the metabolism of a variety of compounds. Humans display genetic variation with respect to acetylation, the population consisting of fast and slow acetylators. The responsible liver enzyme, N-acetyltransferase, is coded for by a single gene. The slow acetylator phenotype is a recessive trait with an approximate 1:1 distribution of slow:fast phenotypes among North American Caucasians and blacks, while among the Japanese there are nine fast acetylators to one slow one (44). Numerous reports in the literature indicate that the ability to acetylate is associated with increased susceptibility to a number of acetylatable nitrogen compounds. For example, when acetylated metabolites have proved to be more toxic than the parent compound, the fast acetylator is the individual at increased risk (5,86). On the other hand, individuals with the slow acetylator phenotype have been found to be at considerably increased risk to the development of neurological symptoms associated with the antitubercular drug isoniazid (48), the antidepressant phenelzine (28), the anti-high-blood-pressure agent hydralazine (100), sulfa drugs, and the anti-leprosy drug, dapsone, presumably because of lack of ability to detoxify these substances by N-acetylation.

Humans are able to deactivate arylamines by acetylation, thus inactivating a class of potent bladder carcinogens. Persons who are fast acetylators have about 9 to 10 times more acetylase activity than the "slow" individuals (38).

Lower, et al. (81), hypothesized that humans with the slow acetylator phenotype would be at increased risk to develop arylamine-induced bladder cancer. Their preliminary epidemiologic study supports this hypothesis. The authors reported that a population of urban urinary bladder cancer patients exhibited a small excess of individuals with the slow acetylation phenotype as compared to a control group. Lower, et al. (81), did not investigate the most ideal population to test this theory, since the selection of patients did not involve persons occupationally exposed to arylamines. Furthermore, the study had important methodological limitations in that potential confounding variables such as smoking and occupation were not controlled.

Since 50 percent of the North American Caucasian and black populations are slow acetylators, the sheer number of those at potential increased risk is striking. Currently, the theory is well founded in cancer research with a variety of animal models (81). However, additional epidemiologic studies of populations with bladder cancer are needed to follow up the preliminary evidence that the degree of risk for such cancer depends on one's ability to acetylate arylamines. A Japanese study is being organized to test this hypothesis (82). The Japanese are particularly suited for this study because of the low prevalence of the slow acetylator phenotype in that population and the availability of a group of former workers exposed to high levels of arylamines in past decades (Omenn, personal communication).

HLA and disease associations

Just as each individual has his or her own unique fingerprints, it is now known that each individual also has a biochemical fingerprint determined by the presence of specific proteins on the surface of cell membranes. This array of cellular surface proteins has been best studied with leukocytes and is called the human leukocyte antigen (HLA) system (83). Several striking associations between many human diseases and various HLAs have been revealed (6,24,109,118). For instance, the antigen B27 has been associated with ankylosing spondylitis (a disease that causes spinal immobility) and the antigen B8 with thyroid disease.

These antigens are coded by a set of very closely positioned genes. Since each person inherits a total of 10 HLA genes, the number of possible antigen combinations is in the hundreds of millions (46).

Despite some striking statistical association of certain diseases with specific HLAs, any mechanistic relationship is yet to be uncovered, thereby precluding at present the possibility of knowing whether the relationship is causal or only associational. Nevertheless, the recognition of the statistical relationships of HLAs with a wide range of human diseases suggests that inherent genetic factors are affecting the occurrence of the diseases within the population.

At present, there is not enough information to suggest the use of HLA typing in an occupational setting, but this simple test may in the future be used to indicate classes of chemicals to which a person is likely to be susceptible.

Carbon oxidation

Numerous drugs and environmental pollutants are metabolized in part via oxidation. The metabolic significance of this process is profound because oxidation may result in a metabolite either more or less toxic (or carcinogenic) than the parent compound. Interspecies differences in the ability to oxidize various compounds have resulted in differences in toxic and carcinogenic responses. For example, the inability of guinea pigs to oxidize aromatic amines is thought to explain their lack of susceptibility to developing cancer from these compounds.

Among humans, individual variations exist with respect to the metabolism of certain drugs. The magnitude of these differences may be considerable. For instance, a 20,000-fold variation in the metabolism of debrisoquine has been reported (49). Such differences help to explain the wide variation in the optimal dose requirement of debrisoquine (20 to 400 mg/day) to control blood pressure in hypertensive patients, a phenomenon of considerable clinical significance.

Experimental studies have revealed that the ability to oxidize drugs such as debrisoquine is controlled by a single gene, with the low activity being recessive. Limited experimental evidence suggests that the frequency of the low activity gene in the population varies markedly according to the ethnic group (Caucasian-British, 5 percent; Egyptian, 1.5 percent; Nigerian, 15 percent; and Ghanaian, 12 percent). A report studying Nigerians has suggested that low activity oxidizers may have a decreased frequency of bladder cancer from aflatoxin, a compound known to require activation to become a carcinogen (50). Heterozygous individuals, who display an intermediate oxidation capability, are predicted to represent about 50 percent of the population if homozygous recessive individuals make up 6 percent of the population (49).

The occupational and environmental health implications of these findings are notable. For example, many known mutagens and/or carcinogens require an initial activation step via an oxidative process. The extent to which humans differ in their ability to activate potential toxic or carcinogenic compounds may contribute significantly to explaining the variation in population responses to such agents. In addition, the number of potentially affected people is enormous.

Diseases of DNA repair

There is a group of heritable traits* in which a DNA repair defect has been proved or strongly implicated. Moreover, an increased frequency of chromosomal abnormalities is found in the lymphocytes of these individuals (with the exception of xeroderma pigmentosum). Affected individuals also are at increased risk for certain cancers, further linking chromosomal abnormalities with cancer (7,36,61,73,108,113). The diseases, all results of homozygous recessive traits, cause overt illness and are not compatible with a normal lifestyle. On the other hand, it is possible that the heterozygous conditions which show no clinical manifestations could lead to increased susceptibility to toxic chemicals or ionizing radiation in an occupational setting.

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*Xeroderma pigmentosum (XP), ataxia telangiectasia (AT), Fanconi's anemia, and Bloom's syndrome.

Individuals heterozygous for these traits have normal frequencies for chromosomal aberrations and SCEs (15,32,68). Evidence suggests that these individuals are deficient in particular aspects of DNA repair and consequently may be at higher risk than the general population to DNA-damaging chemicals or radiation. It has been estimated* from the frequency of the homozygotes in the population that the heterozygote frequency may be at least 1 percent. Nonetheless, good tests for identifying those individuals do not exist. The high estimated frequency suggests that many individuals may be at increased risk from occupational exposures.

The four major heritable recessive syndromes of DNA repair also are associated with an increased risk for cancer in homozygous and possibly heterozygous individuals (97,119). The results for heterozygous individuals are not well documented because so few of them have been studied. The types of cancer for which one is at increased risk vary among syndromes and are not specific for any one trait. This suggests that many types of cancer may be caused by, or related to, specific defects in DNA repair. Because many industrial chemicals are known to damage DNA, it is possible that individuals heterozygous for these traits may be at increased risk for disease from exposure to certain chemicals.

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*Using the Hardy-Weinberg equation.

Less well-characterized genetic traits

Other human genetic variants also may put individuals at potential risk to environmental disease. For the most part, these are highly speculative and are of research interest only.

Superoxide dismutase

This enzyme is known to play a critical role in the cell's defense against oxidizing stress. Recently, it has been discovered that genetic variants of superoxide dismutase exist within the human population. The prevalence of the variant allele in the U.S. population is unknown, but, based on a British study in which the heterozygote for the variant was 6.2:1,000 (43), the projected prevalence in the United States may approach 1.2 million. The extent to which this variant alters risk to any oxidizing agents remains to be determined.

Immunoglobulin A deficiency

This genetic condition is known to occur in about 1 in every 400 to 800 persons and is thought to increase the risk of respiratory tract infections (63,64). The extent to which persons with this condition are at increased risk to respiratory irritant gases such as ozone, nitrogen dioxide, and sulfur dioxide remains to be assessed.

Paraoxanase polymorphism

Human blood serum has been found to contain an enzyme, paraoxanase, that hydrolyzes the compound paraoxon, which is the oxidized metabolite of the insecticide parathion. Paraoxanase, coded for by a single gene, displays considerable interindividual variability while its activity remains constant within a given subject (35,101). Approximately 50 percent of the population is thought to be homozygous for the low activity allele, exhibiting one-third to one-sixth the activity of those homozygous for the high activity form (34). An individual with low paraoxanase activity would be expected to be at increased risk to parathion toxicity, although there is no substantiation of this hypothesis.

Pseudocholinesterase variants

There are two types of cholinesterase: acetylcholinesterases (ACHase) and pseudocholinesterase (pACHase). ACHase inactivates acetylcholine (ACH) produced at the neuromuscular junction during neurotransmission. pACHase is found in many tissues as well as blood plasma. While its function is unknown, it has been suggested that it may hydrolyze certain cholinesters which inhibit ACHase (74). While most people have identical pACHase, a number of pACHase variants exist. Most individuals with variant forms typically show no symptoms, but some may exhibit an extreme sensitivity to the muscle relaxant, suxamethonium, because they cannot hydrolyze such substrates as efficiently as those with normal pACHase (25).

Research involving screening of large numbers of humans has revealed that the presence of atypical or variant types of pACHase is under genetic control (56,57). Gene frequencies have been determined for some of the variant genotypes. The most common "atypical" homozygous variant (the dicubaine variant) occurs with a frequency of 1 in 2,800 Canadians of European ancestry (56) and has been found to be extremely sensitive to the insecticide RO2-0683 (74). This is of particular significance in light of the widespread use of this insecticide. Moreover, 3 to 4 percent of the Canadian population tested were found to be heterozygote carriers of intermediate sensitivity (56). Additionally, of the 10 recognized genotypes of pACHase, 4 are known to display a marked sensitivity to suxamethonium. Their combined frequency in individuals of European ancestry is 1 in 1,250 (120).

In terms of public health, the data indicate that individuals have differential sensitivity to the activity of various neuromuscular-acting drugs and insecticidelike chemicals. Differences in sensitivity are directly related to the occurrence of pACHase variants and their diminished ability to inactivate the drug or insecticide analog. Individuals with such pACHase variants should be considered potentially at high risk to anticholinesterase insecticides (75). It should be emphasized that not all drugs and insecticidelike compounds act with greater sensitivity in atypical pACHase variants.

Erythrocyte catalase deficiency

Genetic variants of the red blood cell enzyme, catalase, exist in humans. This has resulted in the grouping of humans into three classifications based on catalase activity levels: normal, hypocatalasemic (50 percent of normal), and acatalasemic (1 to 2 percent of normal). Since red cell catalase facilitates the detoxification of exogenous and endogenous hydrogen peroxide (29), it has been hypothesized that those with a catalase deficiency may be at risk for hydrogen-peroxide-producing agents such as ozone or radiation (12). Since there are an estimated 5 million hypocatalasemics in the United States, it would be important to assess any differential susceptibility this group may exhibit toward such stressor agents.

Dermatological susceptibility

Dermatitis is the single largest cause of occupational disability (104). Susceptibility to irritants is known to vary widely among individuals, and both primary irritant and allergic contact dermatitis are probably dependent on genetic factors. Yet, with the possible exception of some HLA correlations, these genetic factors have yet to be identified. Therefore, it is not now possible to genetically screen individuals for their susceptibility to industrial chemicals. On the other hand, a dermatological problem is easily noted and the offending chemical can be isolated.

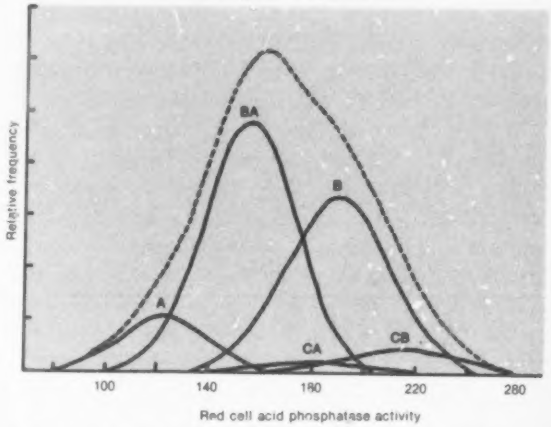
Conclusions

The identification of genetic factors that may contribute to the occurrence of job-related disease is a science truly in its infancy. Nevertheless, it appears that genetic differences may in part explain a variability of responses to chemicals in the workplace. What percentage of the total variability may be explained by genetic factors is uncertain. The biological foundations of the concept of genetic screening to identify predispositions to occupational disease are sound. In addition, most of the well-studied traits are reliably identified by easy and inexpensive tests. It should be recognized that other biological variables such as age, nutritional status, preexisting diseases, and lifestyle also affect the body's susceptibility to a variety of environmental insults. The study of factors affecting susceptibility to occupational diseases, therefore, should not stop with a quantification of genetic influences, as important as they may be, but also should incorporate the other biological variables.

Most variants discovered thus far are rare, with frequencies of less than 1 per 1,000. The benefit/cost ratio of screening for those who possess rare alleles that predispose to disease could well be negative. Screening for variants that occur in at least 1 percent of the population is more likely to be cost beneficial. The following reservations apply to screening for evidence of prevalent variants as well as rare alleles:

- Screening tests might not be capable of distinguishing with high specificity and sensitivity one variant from another or from the predominant allele (if one exists). When more than one allele exists, the number of possible different enzymes in the population, each of which may have a mean activity different from the others, exceeds the number of alleles. The distribution of the activities of these different enzymes may overlap. For example, three alleles of the gene for red blood cell acid phosphatase have been found in the English population. The distribution of phosphatase activity in the population, which follows a fairly smooth unimodal distribution (45) (see fig. 8), is accounted for by the overlapping distribution of the activities of five of the six different enzymes that would be expected from three alleles. In screening for acid phosphatase activity, many classification errors would be made regardless of the cutpoint.

Figure 8.—Distribution of Red Cell Phosphatase Activities in the English Population



SOURCE: H. Harris, *The Principles of Human Biochemical Genetics* (Amsterdam: North-Holland Publishing Co., 1977).

- Where continuous, unimodal variation in enzyme activity in a population is observed, the chance of disease in response to an environmental agent also might vary continuously, correlating approximately with the amount of enzyme activity. Thus, even if it were possible to distinguish those who possess one allele from those who possess another, it might not be appropriate to dichotomize the population into two categories of those at high risk of disease and those at low risk.
- The chance that a person with a specific allele will develop disease on exposure may depend on the presence of other factors, some genetic and some environmental. For instance, the slow acetylator phenotype may explain only a small percentage of the bladder cancer variance within the population.
- Despite the high degree of genetic diversity, and possibly even of differences in enzyme activity conferred by different alleles at a locus, allelic differences may not be associated with differences in susceptibility. Different alleles may coexist precisely because they do not differ in the biological fitness they confer. Their respective frequency may depend on random genetic drift from one generation to the next.

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Priorities for future research

Well-designed, prospective epidemiologic studies are needed to assess the correlation between specific genetic traits and predisposition to illness. A major weakness in several important existing studies (59,60,81) is that both clinicians and laboratory research scientists have attempted to conduct epidemiological research studies without the apparent assistance of persons specifically trained in epidemiological research methodology. Unless the epidemiologist is involved in the initial design of the study as well as in subsequent analysis procedures, there is a serious likelihood that expensive and time-consuming research will yield far less valuable and defensible data.

During epidemiological studies, researchers could acquire HLA profiles when appropriate. This would begin to provide a greatly expanded data base which would be useful in understanding the associations of HLA markers with environmentally related diseases.

Red blood cell traits

Given that these traits are prevalent in the population and that many potential hemolytic and oxidizing chemicals are employed in a wide variety of industries, there is a clear need to assess whether individuals with traits potentially predisposing susceptibility to these chemicals are indeed at risk. Two approaches to this assessment could be undertaken.

Research could be initiated on the development of a predictive animal model that would simulate the response of human red blood cell deficiencies. This would allow for the rapid evaluation of large numbers of potential hemolytic compounds singly or in combination under precise exposure conditions. It would also assist in providing direction for epidemiologic research studies. An animal model recently has been developed in which guinea pigs are transfused with human red blood cells, thus overcoming interspecies differences. Using this model, chemical exposures can be done and the responses of the red blood cells monitored. Human red blood cells have been shown to survive in the animals for 2 to 4 days, allowing some good, preliminary experiments to be done.

The second approach involves epidemiological research studies in appropriate industries where hemolytic and oxidizing agents (and benzene and lead) are used and where exposures approach Federal limits. Such research should attempt to differentiate the susceptibility of the A− and Mediterranean variants for G-6-PD deficiency. The studies also should assess any possible synergistic interaction between medications and hemolytic industrial chemicals.

Differential metabolism of industrial/ pharmacological compounds

Further documentation of the extent to which humans differ both qualitatively and quantitatively in metabolizing foreign compounds is needed. More specifically, further work on genetic variants of carbon oxidation and AHH could be conducted. The research should involve not only a genetic component but nutritional and aging considerations as well. Results from such studies should contribute markedly to the present understanding of idiosyncratic drug reactions as well as the occurrence of differential susceptibility to environmental toxins. These studies may involve a wide variety of chemical agents including drugs or industrial or commercial products.

In addition, methods for measuring AHH inducibility which are reproducible in different laboratories need to be developed.

Epidemiologic investigations are needed to assess the risk of individuals with the slow acetylator phenotype for developing arylamine-induced bladder cancer. Since the slow acetylator represents about 50 percent of the population, the population at risk is extremely large. As in the case of the other complex disease processes, arylamine-induced bladder cancer is affected by a variety of factors in addition to acetylator phenotype. Some confounding metabolic variables may include the capacity to N-hydroxylate the arylamine and the capacity to deacetylate an acetylated compound. Moreover, factors such as age and sex need to be recognized.

It has been hypothesized that slow acetylators are at greater risk of developing arylamine-induced bladder cancer than fast acetylators. However, the extent to which people differ in their ability to deacetylate previously acetylated arylamines can markedly affect the outcome of studies designed to test the original hypothesis. Deactylation capability varies widely among species and affects susceptibility to carcinogens. The extent to which humans differ in this regard is not known.

SAT deficiency

Research could be conducted on the relative contributions of SAT levels and other factors thought to help cause development of emphysema. Data are needed to validate recent studies that suggest that ozone exposure at ambient summertime levels and cigarette smoking may result in a marked reduction in SAT levels.

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Chapter 8

Legal Issues Raised by Genetic Testing in the Workplace

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Chapter 8

Legal Issues Raised by Genetic Testing in the Workplace

Genetic testing raises many legal issues for which there are few clear answers. The most fundamental question is whether the technology is compatible with existing laws and the established legal rights of employees. This question embodies a number of issues within the broad spectrum of employee-employer relations, ranging from the nature of the doctor-employee relationship through the proper use of the test results to the employer's responsibility to prevent occupational illness. These questions may be specified as follows:

- Who has the legal responsibility for achieving and maintaining a safe workplace?
  —What does "safe" mean?
  —How is safety to be achieved?
- To what extent does the law protect the interests of individuals or groups who may be at increased risk of occupational illness?
- When, if ever, does an employer have a duty to use certain medical procedures, including genetic testing?
- What are the legal constraints on occupational medical testing procedures, whether used routinely or for research?
  —What information must be given to the employee?
  —What use can be made of the results?
- What are the employer's rights to use employee selection methods that it deems appropriate?
- Under what circumstances could the Occupational Safety and Health Administration (OSHA) require medical tests in general and genetic testing in particular?
- To what extent can employers and employees or their unions negotiate their own answers to these questions?

No Federal statute specifically covers or even refers to genetic testing in the workplace. No Federal court cases have dealt with the subject. Consequently, there are no direct legal precedents to guide decisionmaking. However, there are many established legal principles governing the rights and duties of employers, employees, company medical personnel, and unions. These can be applied to the issues raised by this new technology.

There are three major ways that legal rights and duties governing employer-employee relations are created. The first is by judicial decision, which produces a body of legal principles known as the common law. The second is by legislative decree. Federal and State statutes can expand, modify, or overturn common law rights and duties or create new ones. The first major example of this in employer-employee relations was the enactment of workers' compensation laws by all of the States in the first part of this century. Other applicable statutes include the National Labor Relations Act (NLRA), the Occupational Safety and Health Act of 1970 (OSH Act), the Civil Rights Act of 1964, and the Rehabilitation Act of 1973. The third way is by contractual arrangements between employers and unions. These are known as collective bargaining agreements and are authorized by the NLRA. Rights and duties with respect to company employment and medical practices may be created, modified, or enhanced by collective bargaining agreements so long as they are not incompatible with existing law.

These sources of law provide a useful framework for addressing the legal issues raised by genetic testing in the workplace.

Basic rights and duties governing employment and medical practices

The common law provided the initial source of legal principles governing relationships among employers, employees, and company physicians. Workers' compensation laws substantially modified the relationship between employer and employee, but the common law continues to be relevant, especially in the doctor-employee relationship and in litigation concerning occupational illness, such as the asbestos cases.

Employer rights and duties

Under common law, an employer had virtually unfettered control in selecting its employees. The employer could hire or refuse to hire for any reason or no reason at all. This right included the right to refuse to hire an individual because of the employer's opinion that the prospective employee was physically incapable of performing the job. Once hired, the employee could be fired "at will" by the employer for any reason or no reason at all, including the employer's belief that the employee could no longer perform the job because of his physical condition. This has been modified by State and Federal antidiscrimination statutes.

Under common law, employers had five main duties for the protection of employees. These were to: 1) provide a safe place to work, 2) provide safe tools and equipment for the work, 3) warn of dangers about which the employee might reasonably be expected not to know, 4) provide a sufficient number of suitable coworkers to ensure the safety of each worker, and 5) promulgate and enforce rules that would make the work safe. These duties are still recognized by the law in the 50 States and the District of Columbia.

An employee who suffered from an injury or illness related to his employment had a right to sue the employer for damages. Because these suits were based on common law negligence,* employers usually were able to escape liability by invoking the common law defenses of contributory negligence, assumption of risk, and the fellow servant rule (53). That is, if the injury or illness was caused in any part by the negligence of the injured worker or any coworker, or if the employee expressly or impliedly assumed the risk of working in a hazardous job, there was no recovery. The concept of assumption of the risk may be relevant in some cases involving genetic testing.

New rights and duties created by workers' compensation laws

Beginning in 1910 with New York, the States took steps to relieve the hardship of industrial accidents on individual workers and their families by passing workers' compensation laws. Today each State has such a statute. The major objectives of these laws are to: 1) provide sure, prompt, and reasonable income and medical benefits to work-accident victims, or income benefits to their dependents, regardless of fault; 2) provide a single remedy and reduce court delays, costs, and workloads arising out of personal injury litigation; 3) eliminate payment of fees to lawyers and witnesses, as well as the expense of time-consuming trials and appeals; 4) encourage maximum employer interest in safety and rehabilitation through an appropriate experience-rating mechanism; and 5) promote study of the causes of accidents in order to prevent future accidents (66).

Workers' compensation is a form of "strict liability" whereby the employer is charged with the injuries arising out of its business without regard to fault. Common law damage actions* are precluded, but so too are common law defenses. The employee is assured of medical expenses and income maintenance; employers are protected against potentially large personal injury judgments, including those for "pain and suffering." In addition, employers are assured of relatively fixed production costs that can be passed along to the consumers, since the employer carries insurance to pay workers' compensation claims. Resort to this system is, with some exceptions, the "exclusive remedy" available to injured workers.

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*Negligence is conduct (an act or omission) that involves an unreasonable risk of harm to another person. For the injured party to be compensated, he must prove in court that: 1) the defendant's conduct was negligent, 2) the defendant's actions in fact caused the injury, and 3) the injury was not one for which compensation should be denied or limited for reasons of overriding public policy.

Virtually all private sector employees are covered by State workers' compensation laws and government employees are protected by similar laws. Where the statute does not apply, injured employees retain their common law rights and remedies.

Each State law sets its own eligibility requirements, benefit levels, and administrative mechanisms for claims processing. The resulting wide range in eligibility and benefit levels is one of the most frequent criticisms of workers' compensation.

One of the most troubling aspects of worker's compensation law is in dealing with occupational disease. Claimants must prove that the disease from which they suffer is work related and not one of the "ordinary diseases of life" (41,62). This is extremely difficult to do for many occupational diseases, which have long latent periods and whose causes are poorly understood. Consequently, occupational disease cases are six times more likely to be contested than accident or other cases (32), and relatively few claimants prevail (7).

Exceptions to the "exclusive remedy" rule

There are a number of exceptions to the general statement that workers' compensation is the only remedy available to an employee suffering from work-related injury or illness. Two of the exceptions are most relevant here.

DUAL CAPACITY

In a minority of jurisdictions, an employer may become liable to its own employee if the employee's injury or illness resulted from the breach of a duty arising outside the scope of an employer-employee relationship. In these situations the employer is said to be acting in a "dual capacity." The most important of these for genetic testing is when an employer provides medical services, whereby it incurs the risk of medical malpractice claims.

One category of these claims involves the failure of the company physician to detect or to inform an employee of illness. For example, in *Bednarski* v. *General Motors Corp.,** a wrongful death action** was permitted to be brought based on the company's failure to diagnose or to inform the plaintiff's decedent that he had lung cancer, even after performing a series of physical examinations and X-rays. Many of these failure to diagnose or inform cases are based on non-work-related illnesses that were allegedly detectable during preemployment examinations (8,9,73).

An employer might also be found liable for negligently failing to discover an employee's propensity to contract a work-related illness, thereby permitting the employee to be exposed to conditions that bring about the disease (14,56). If such a case were brought, however, the plaintiff would be required to prove that a reasonably prudent company doctor exercising ordinary skill and judgment would have detected the employee's likelihood of contracting an occupational disease. It is unlikely, at least at the present time, that an employer would be liable where the employee's medical condition could only be detected through sophisticated biochemical or cytogenetic procedures and the employer did not use these procedures. On the other hand, the negligent misuse of these procedures by the employer might provide the basis for liability.

Two other points related to dual capacity medical malpractice are relevant. First, even where the examining physician is not negligent, the employer may be liable if established company medical practices are inadequate (36). Second, in some jurisdictions the company physician may be sued individually for negligence and is not protected by the employer's immunity under workers' compensation laws (30,31).

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*The term "action" is synonymous with suit or lawsuit.

*88 Mich. App. 482, 276 N.W.2d 624 (1979). Accord, *Hoover* v. *Williams*, 203 A.2d 861 (Md. 1964) (silicosis).

**A wrongful death action is a suit claiming that the defendant's conduct wrongfully caused someone's death and that the plaintiff, usually the surviving spouse or children, was harmed as a result.

WILLFUL AND INTENTIONAL TORTS*

In almost all jurisdictions, an exception to the exclusive remedy rule is recognized if the employee can prove that the employer specifically intended to harm him (4,35,59). This is a fairly high hurdle for a plaintiff employee to clear. In *Mandolidas* v. *Elkins Industries, Inc.*,** however, the West Virginia Supreme Court of Appeals greatly expanded the rule and held that an employer is liable for employee injuries resulting from the employer's willful, wanton, or reckless misconduct: "[W]hen death or injury results from willful, wanton or reckless misconduct, such death or injury is no longer accidental in any meaningful sense of the word, and must be taken as having been inflicted with deliberate intention for the purposes of the workmen's compensation act." A recent Ohio case also adopted this viewpoint (11).

The *Mandolidas* case could arguably support an action against an employer by an employee if the following conditions were met: 1) the employer was using genetic screening tests, 2) the tests were highly predictive, 3) the tests identified the employee as susceptible, 4) the employer placed an employee into a high risk instead of a low risk environment, and 5) the employer contracted the disease for which he was identified as being at risk.

A more substantial body of law exists to allow recovery for injury or illness caused by the fraud or deceit of the employer. The cases usually involve concealment of an existing illness. For example, where employers have fraudulently concealed from employees the fact that they were suffering from lung cancer (37) or silicosis (21), the employees were permitted to bring damage actions for injuries caused by the aggravation of their initial condition. There is also some limited case law to the effect that fraudulent concealment of information about hazardous working conditions would permit an injured employee to recover damages (34). These cases on fraudulent concealment might support an action where the concealment involved the results of genetic monitoring, if the results validly predicted that employees were at an increased risk of developing cancer and the plaintiff developed cancer.

Products liability

The "exclusive remedy" provisions of workers' compensation laws apply only to actions brought by injured employees against their employer. Some jurisdictions permit suits against other companies, for example, the manufacturer of a product used by the employee on the job. This products liability litigation—where the employee alleges that an injury or illness was caused by a product manufactured by the defendant and supplied to the employee's employer—is rapidly expanding. Perhaps the best known type of case, and certainly the most prevalent number of these cases, involves asbestos.

Asbestos and other products liability suits often are based on the allegation that the manufacturers failed to warn all those who might handle the product of its hazardous nature. In the leading case of *Borel* v. *Fibreboard Paper Products Corp.*,* the Fifth Circuit Court of Appeals accepted such a claim by ruling that the defendant manufacturer of insulation material that contained asbestos had a duty to warn all users of its asbestos products, including insulation workers who did not make the product but simply installed it, of the foreseeable dangers associated with handling asbestos.

Products liability conceivably could become an issue for genetic testing. For example, if a company manufactured a chemical that was a suspected carcinogen, it might feel compelled to use cytogenetic monitoring to help it determine the potential hazards associated with the chemical, not only to protect its employees but also to be able to warn its customers' employees. Failure to take such steps might provide grounds for lawsuits similar to those for asbestos.

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*A tort is a civil wrong, other than breach of contract, for which a court will award damages or other relief.

**246 S.E.2d 907 (W. Va. 1978).

*493 F.2d 1076 (5th Cir. 1973), *cert. denied* 419 U.S. 869 (1974).

Rights and duties in company medical practices

THE DOCTOR-EMPLOYEE RELATIONSHIP

The nature of the doctor-employee relationship is clouded by the dilemma of the conflicting duties of the occupational physician. On one hand, the doctor is an employee of the company and thus has the duty to further the company's interests. On the other, when the doctor examines or treats employees, this interaction looks very much like the standard doctor-patient relationship.

The tension between the doctor's conflicting duties may be seen in the following example. Suppose a person's annual checkup by his personal physician reveals a condition that would make him susceptible to disease in a certain work environment. The doctor has the duty to inform the patient of the risk, and the patient can choose to act on that information as he sees fit. If, however, the examination was a preemployment one conducted by the company physician, the doctor's primary duty would be to inform the employer, with the likely result that the person would not be hired or would be placed in a job different from the one for which he was originally considered.

It is important to determine whether a physician-patient relationship exists between an employee and an employer-provided doctor. If there is no such relationship, the doctor owes no duty to the employee except to use ordinary care not to injure the employee during the course of the examination. If there is a physician-patient relationship, the physician must render medical care with the skill and learning commonly possessed by members of the profession. The physician also would have the following legal duties: 1) to discover the presence of disease, 2) to inform the patient of the results of the examination and of any tests performed, 3) to advise the employee of risks associated with continued exposures, and 4) to preserve the confidentiality of communications and records.

The traditional view is that there is no physician-patient relationship between an actual or prospective employee and an employer-provided doctor (2,39,58). Courts that adhere to the dichotomy between employer-provided and traditional patient-obtained medical care look to whether the physician is treating or merely examining the individual or for whose benefit the physician is performing the service. If the physician is merely examining the individual or performing services for the benefit of the employer, no physician-patient relationship will be found.

There are indications that this is changing, and the current state of the law is less certain (49). The distinction between treating and examining seems simplistic and artificial. Occupational physicians examine and treat; the benefit of their services goes to both employer and employee. Therefore, to determine if there is a physician-patient relationship, other factors also need to be considered, including whether there is an ongoing medical relationship between the parties or merely a single examination, what the reasonable expectations of the physician and patient are as to the nature of the examination, whether any diagnosis or treatment is contemplated by the examination, and the nature of the employee's consent to the examination. In fact, the employee's expectations as to the nature of the exam may create a duty on the part of the employer's physician to inform potential employees of any serious health problems that the doctor discovers or should have discovered with the exercise of reasonable care. This duty would arise not out of a physician-patient relationship per se, but out of the natural reliance by the potential employee on the physician to inform him of any uncovered health problems. Acting on this reliance, the applicant may forego additional examinations to his detriment.

THE DOCTOR-EMPLOYER RELATIONSHIP

Unlike the doctor-employee relationship, the relationship between the employer and the doctor is more clear-cut. Generally, the doctor is viewed as representing the employer, and, under the legal doctrine known as *respondeat superior,* actions of the doctor are attributed to the employer. Thus, if the doctor is found to be liable for malpractice or other improper actions with respect to an employee, the employer generally will be held liable too.

DUTY TO CONDUCT MEDICAL OR GENETIC TESTING

Employers are under no general legal duty to conduct preemployment or periodic medical examinations, except where required by OSHA standards covering specific health hazards or pursuant to a provision in a collective bargaining agreement. Nevertheless, approximately 48 percent of all employees in urban workplaces are required to take a preplacement physical examination and nearly 34 percent of all such employees are provided with periodic medical examinations (45).

Under these circumstances, is there a duty to conduct genetic testing during the course of these examinations? The physician has a duty to use reasonable care and customary medical procedures. Since this technology does not meet established scientific criteria for routine use, the physician does not have a duty to use the tests. However, if sufficiently high correlations between genetic endpoints and disease are eventually demonstrated and the tests become a commonly used medical procedure, the occupational physician may have a duty to use them when conducting medical examinations.

EMPLOYEE'S RIGHT TO REFUSE AN EXAM

With the increasing use of occupational medical screening, examinations, and procedures comes the growing likelihood that an applicant or employee would refuse to take such an exam on religious, ethical, medical, privacy, or other grounds. Thus, the question arises whether an applicant or employee has a right to refuse medical tests and still retain his job. Unless the test procedure violates a specific statute, regulation, or collective bargaining agreement, there is no constitutional or common law right to refuse (28).

TESTING SOLELY FOR RESEARCH PURPOSES

An employer may want to conduct genetic tests solely for research purposes, where no job actions are taken with respect to employees. In this situation, absent a specific provision in a collective bargaining agreement, it would appear that the employee has no right to refuse to take part in the testing and still retain his job. Research on methods to determine the health effects of workplace exposures can be a valid condition of employment.

There are constraints on how the research may be conducted. If an employer had received Federal funds for the research or were conducting the research with a university that had received Federal funds for the project, the researchers are required by the National Research Act* to establish an Institutional Review Board (IRB) in order to protect the rights of the human subjects. The Department of Health and Human Services (DHHS) has promulgated regulations which, among other things, specify the criteria for IRB membership and approval of the research.** One of the most important of the criteria for approval is that informed consent to the research must be given by each subject. While the regulations specify at least eight elements of informed consent, these elements basically condense to the following requirements: 1) all of the important information, such as the procedures, the risks, and the possible benefits, must be disclosed to the employee in terms he or she can understand; 2) the employee must understand that information; 3) the employee must be mentally competent to consent; 4) the consent must be voluntary; and 5) a statement must be provided describing the extent to which confidentiality of records identifying the subject will be maintained. A further discussion of these regulations is not warranted because most occupational medical research is not likely to be federally funded.

Research to establish the validity of genetic testing most likely will be governed by State law. A few States have enacted statutes covering human experimentation.*** However, State tort law (common law) probably will be the source of applicable law. Tort law generally provides few limitations on such experimentation other than the requirements of informed consent and avoidance of negligence (27). Unlike the elements of informed consent in the DHHS regulations, however, the State-law-developed doctrine of informed consent does not deal with the issue of confidentiality of medical records. Furthermore, in the workplace, the requirements for informed consent are likely to be minimal. Since participation in research can be a valid condition of employment, employees probably would not have to be told much, if anything, about the research, unless it involved a significant risk. Since genetic testing involves low-risk procedures, employees probably would not have to be informed of the tests. Of course, the employee would have to consent to the medical examination in which blood was drawn.

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*42 U.S.C. §2891-3(2) (1976).

**45 C.F.R. §46 (1981).

****See, for example,* N.Y. Pub. Health Law §§2440-2446 (McKinney 1977); Wis. Stat. Ann. §51.61 (West Supp. 1981).

Despite the generally limited legal restrictions on medical research under State law, an employer still might hesitate before embarking on a research program involving genetic testing. An employer may fear that a plaintiff in a lawsuit claiming work-related illness could get access to the results via discovery* procedures and use them to build a better case against the employer, even if the employer believed the results did not establish the validity of the tests.

DISCLOSURE OF HEALTH RISKS

Although a rule** under the OSH Act requires that employees (but not applicants) be given access to their medical records, employers and occupational physicians do not have an affirmative duty under this rule or the common law to disclose the results of medical exams to employees or applicants. However, as noted previously, withholding medical information can give rise to civil liability, where an illness, whether or not occupational, was detected or should have been detected.

This principle possibly could be extended to situations where individuals were merely at risk. Since employers have a common law duty to apprise employees of latent dangers, a company may be liable for failure to disclose that employees are working with a hazardous product. In addition, a physician may be liable for failure to disclose the health risks of the job, if the company gives medical examinations.

Disclosure of information about hazardous substances provides the employer with the opportunity to use the defense of assumption of the risk in lawsuits based on common law theories of negligence. That is, if an employee who was at increased risk of disease knowingly placed himself in the risky environment, he could not later sue the employer or physician for negligence if he developed the disease (13,72).

EMPLOYEE ACCESS TO MEDICAL RECORDS

In view of their concern about possible misuse of information from genetic screening and a likely desire to know of risks to their health, employees and applicants might want to have access to their medical records. As of 1980, employees have a right to see their medical records pursuant to OSHA's Access to Employee Exposure and Medical Records Standard.* Besides OSHA's access standard, which applies only to toxic substances and which is still being challenged in the courts, there are few legal requirements that employers give employees a right of access to medical records. Five States—Connecticut, Massachusetts, Maine, Ohio, and Wisconsin—provide for such a right, usually as part of a broader right to review the employee's entire personnel record.** Applicants have no rights to company medical records. The only other source of an access right is through a collective bargaining agreement.

CONFIDENTIALITY OF MEDICAL RECORDS

One concern of employees or applicants who have been genetically screened would be to prevent the spread of embarrassing, damaging, or false information about themselves, particularly to other potential employers. Thus, they would wish to know to what degree such information would be kept confidential.

The Code of Ethics for Physicians Providing Occupational Medical Services provides that "employers are entitled to counsel about the medical fitness of an individual in relation to work but are not entitled to diagnoses or details of a specific nature." In practice, however, management access to employee medical records is often much more extensive (49,55,70).

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*Discovery is the right of parties in a lawsuit to have access to information in the possession of their adversary relevant to the suit. This right of access is quite broad. The theory underlying discovery is that the parties should not be "ambushed" at trial by information that was previously unknown to them and detrimental to their case.

**29 C.F.R. §1910.20 (1981).

*45 Fed. Reg. 35,212-35,303 (May 23, 1980), *codified at* 29 C.F.R. §1910.20 (1981).

**Conn. Gen. Stat. Ann. title 31, §128c (West Supp. 1981); Mass. Ann. Laws ch. 149, §19A (1976); Me. Rev. Stat. Ann. title 26, §631 (West Supp. 1981); Ohio Rev. Code §4113.23 (Page 1980); Wis. Stat. Ann. title 13, §103.13 (West Supp. 1981).

There are few legal restrictions on such disclosures within the company. Often as a condition of employment, employees sign blanket waivers authorizing the company to use medical and personnel records as it deems necessary. Even if a waiver is not signed, it has been asserted that "workers have little genuine expectation of true confidentiality as to employment medical records" (49). In one case, the court stated that the employment exam "was wholly for the benefit of the Company, and the doctor owed to it alone the duty to perform efficiently the work the Company had employed him to do. Appellant must be charged with knowledge of this" (39). Thus, there was an implied waiver of confidentiality by the employee's consenting to the examination. Finally, liability for wrongful disclosure would have to be based on a breach of the physician's duty of confidentiality and, as discussed earlier, many courts have found that there is no physician-patient relationship where the physician is provided by the company.

With respect to disclosure of medical information to parties outside the company, there are also few restrictions under common law. In any lawsuit alleging damage from such disclosure, the plaintiff would have to overcome the defense that there was no duty of confidentiality because there was no doctor-patient relationship between the company physician and the employee or job applicant (54).

Some State and Federal statutes provide a variety of protections from disclosure. OSHA's access standard gives OSHA the right to employee medical records in personally identifiable form, but limits the disclosure of such information and provides safeguards to ensure confidentiality. The DHHS regulations on human experimentation require, "where appropriate," adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.*

The most extensive regulation of medical information is California's Confidentiality of Medical Information Act.** It requires employers who receive medical information to establish procedures to ensure its confidentiality. Further, employers cannot disclose this information to others without the employee's written consent.

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*45 C.F.R. §46.111(a)(7).

**Cal. Civ. Code Ann. §56 (Deering Supp. 1982).

Statutory regulation of company medical and employment practices

Three Federal statutes—the Occupational Safety and Health Act of 1970, the Civil Rights Act of 1964, and the Rehabilitation Act of 1973—are directly applicable to medical and employee selection practices used by employers. The OSH Act* was enacted "to assure so far as possible every working man and woman in the Nation safe and healthful working conditions . . . ."** The act provides the Government with broad regulatory authority over physical conditions in the work environment. Since genetic testing may play a role in the prevention of occupational illness, questions naturally arise about whether genetic testing is or could be required, prohibited, or otherwise regulated pursuant to the act.

Title VII of the Civil Rights Act of 1964, as amended,* and sections 503 and 504 of of the Rehabilitation Act of 1973** govern employment rights. Title VII prohibits employment discrimination on the basis of race, color, religion, sex, or national origin. The Rehabilitation Act prohibits employment discrimination against otherwise qualified handicapped individuals by employers who are Government contractors or recipients of Federal assistance. These statutes embody the policy that individuals are not to be discriminated against on the basis of immutable characteristics and that their abilities are to be judged on an individual basis. Since one major type of genetic testing—genetic screening—could result in employment discrimination against classes of individuals with particular inherited traits, the question arises as to whether such discrimination is prohibited by these two acts.

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*29 U.S.C. §§651-678 (1976 & Supp. III 1979).

**§2, 29 U.S.C. §651 (1976).

*42 U.S.C. §2000e (1976 & Supp. II 1978).

**29 U.S.C. §§701-796 (1976 & Supp. III 1979).

This question is not answered simply by asserting that the OSH Act requires every employee, even those who may be genetically susceptible to illness, to have a safe working environment and therefore federally mandated exposure levels of hazardous substances must be low enough to protect these people. The broad policy of worker protection embodied in the act is limited by requirements that Government exposure standards be technologically and economically feasible and that they be imposed only after a finding of a significant risk of material health impairment. Thus, there is a tension between the social goals of maximizing equal employment opportunity and safety in the workplace.

This section examines how these three statutes and State fair employment practices laws deal with the sometimes conflicting policy goals and various legal questions created by genetic testing.

Occupational Safety and Health Act

The OSH Act is the only comprehensive statute addressing hazards in the workplace and therefore is the primary vehicle for hazard elimination in that setting. Section 5(a) of the act requires employers to furnish a place of employment free from recognized hazards and to comply with all standards promulgated under the act. "Recognized hazards" has been interpreted by the courts to mean recognized by the employer or the industry and that there is a recognized way of dealing with it; that is, it is preventable (46). Section 5(b) requires each employee to comply with "all rules, regulations, and orders issued pursuant to this Act which are applicable to his own actions and conduct."* Despite the seeming similarity of these provisions, it is clear that "[f]inal responsibility for compliance with the requirements of this Act remains with the employer" (60). Employees cannot assume the risk with respect to health and safety hazards as they could under common law. Only the employer may be issued citations, assessed penalties, and ordered to abate violative conditions. Employees may only petition the Secretary of Labor to enforce the requirements of the act; the employer is required by law to obtain the compliance of employees, even if this entails disciplining disobedient employees. Violations of the act or rules promulgated thereunder can result in civil or criminal penalties against the employer. The act does not supersede or affect rights and duties created by common law or workers' compensation statutes.

Employer duties under the OSH Act are specific and nondelegable. An employer may not rely on a union to provide safety training, and it may not shift the burden of compliance to employees or supervisors. Under the act, employees may not assume the risk nor consent to work in conditions that violate the act's requirements.

An important right of employees under the OSH Act is the right to refuse to work under extremely hazardous conditions where there is insufficient time to eliminate the hazard by resort to regular enforcement channels. This right, based on the broad antidiscrimination provision in section 11(c), was established in an OSHA regulation,* which was unanimously upheld by the Supreme Court in *Whirlpool Corp.* v. *Marshall.***

If cytogenetic tests showed an increased number of chromosomal abnormalities in one or more employees, could they walk off the job? The answer is probably not. First, because of the debatable predictive ability of these procedures, it is unlikely that the employee or employees could demonstrate the regulation's requirement that there be a "real danger of death or serious physical injury." Second, and more important, most occupational illnesses are developed over a period of time. Therefore, it is likely that the employee would fail to meet the "imminence" or "urgency" requirement of the regulation. To date, all of the work refusal cases have involved safety hazards.

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*§5(b), 29 U.S.C. §654(b) (1976).

*29 C.F.R. §1977.12(b)(2) (1981).

**445 U.S. 1 (1980).

Given the employer's duty under the OSH Act to maintain a safe workplace, is genetic testing compatible with or contrary to that duty? To answer this question, it is necessary to consider several more specific questions that are focused on the particular types and applications of genetic testing and the various requirements that can be imposed on employers pursuant to the act. These are addressed in the remainder of this section.

GENETIC TESTING AND THE GENERAL DUTY CLAUSE

The first clause of section 5(a) of the OSH Act, which requires employers to maintain a workplace free from recognized hazards, is known as the general duty clause. Does it require employers to use genetic monitoring to identify hazards? Does it require or permit the use of genetic screening to identify potentially susceptible workers?

The general duty clause simply imposes a requirement on employers without stating the means by which that requirement can be met. Thus, it would not support an argument that genetic testing is required by the OSH Act. Neither would it support an argument that genetic testing is prohibited by the act. Although genetic testing could be adverse to the interests of particular employees, it certainly would not be a "hazard." These conclusions, however, leave open the question of whether OSHA can require, prohibit, or regulate genetic testing under its power to set safety and health standards.

EMPLOYEE VARIABILITY IN STANDARDS SETTING

Section 5(a)(2) of the OSH Act gives the Secretary of Labor broad power to require a safe workplace by setting standards that can govern virtually all aspects of the work environment in any way related to safety or health. The standards may be promulgated in one of three ways. First, under section 6(a), the Secretary of Labor was initially authorized to adopt without rulemaking proceedings "established Federal standards" developed under other Federal acts and "national consensus standards" produced by nationally recognized, private standards-producing organizations. This special authority, which expired in 1973, was included in the act to ensure that workers would be protected as soon as possible after the act's effective date. Second, under section 6(b), new standards may be promulgated by following certain rulemaking procedures. Third, emergency temporary standards may be promulgated under section 6(c) without rulemaking procedures if certain conditions are met.

In 1971, pursuant to section 6(a), OSHA adopted as established Federal standards 450 threshold limit values (TLVs) developed by the American Conference of Governmental Industrial Hygienists (ACGIH). By definition, TLVs do not consider employee variability, but set levels to which "healthy" workers may be exposed without adverse health effects.* These TLVs still form the backbone of OSHA health standards, with only 21 additional health standards having been promulgated under section 6(b) during OSHA's first 10 years.

Section 6(b)(5) provides that in promulgating standards regulating toxic substances or harmful physical agents the Secretary must set standards to ensure, to the extent feasible, that "*no* employee" will suffer material impairment of health or functional capacity, even if exposed for his or her entire working life.** Based on this seemingly absolute language and because of the wide variability in human susceptibility to occupational disease, it might be assumed that OSHA has the authority and in fact is required to promulgate health standards that protect even the most susceptible worker. However, does this mean that OSHA must adopt standards that will ensure that a blind person can drive a truck without suffering an impairment? Does farm work in the Sun Belt have to be made safe for a person with xeroderma pigmentosom, a genetic defect that creates an increased risk for skin cancer?

There are two limitations on the broad language of Section 6(b)(5), one in the section itself and the other imposed by a recent Supreme Court decision. The first limitation is that employees can be protected only to the "extent feasible." This language was interpreted in a recent Supreme Court case, *American Textile Manufacturers Institute* v. *Donovan* ("the *Cotton Dust* case").* At issue was an OSHA standard governing employee exposure to cotton dust. The standard contained many different provisions, some of which the Court struck down and some that it upheld. In upholding the provisions setting exposure limits to the dust, the Court ruled that the phrase "extent feasible" does not require or permit OSHA to perform a cost-benefit analysis of the impact of its standards but does require that the standards be technologically and economically feasible. By "technologically feasible," the Court meant capable of being done, and by "economically feasible" it meant feasible for the industry but not necessarily for individual companies. The exposure limit provisions met these requirements. In setting the limits, OSHA acknowledged that 12.7 percent of exposed employees would still suffer from the ill effects of exposure to cotton dust.

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*A TLV represents the maximum time-weighted average concentration to which a healthy worker may be exposed for a normal 40-hour week up to 8 hours a day over a working lifetime (40 to 50 years) without becoming ill (1).

**29 U.S.C. §655(b)(5) (1976) (emphasis added).

The second limitation on the language of section 6(b)(5) was imposed by the Supreme Court in *Industrial Union Department, AFL-CIO* v. *American Petroleum Institute* ("the *Benzene* case").** The industry had challenged an OSHA standard that had lowered the permissible exposure limit (PEL) for benzene from 10 parts per million (ppm) to 1 ppm, a level that OSHA had determined to be feasible. The plurality opinion, concurred in by four of the nine Justices, held that the Secretary of Labor must determine on the basis of substantial evidence that a standard "is reasonably necessary or appropriate to remedy a significant risk of material health impairment." The opinion stated further that the OSH Act "was not designed to require employers to provide absolutely risk-free workplaces," but was only intended to require "the elimination, as far as possible, of significant risks of harm."

From the above discussion, it is clear that OSHA can and must set exposure limits to toxic substances or harmful physical agents that protect susceptible individuals, but only to the extent that it finds that exposures above the limit present a significant risk of material health impairment and that the limit is technologically and economically feasible.* A question unresolved in the *Benzene* case is whether significant risk is to be measured with respect to each individual or on some group basis. In other words, it is unclear whether OSHA could promulgate a PEL designed to protect a very small number of susceptible individuals or if it first must find a significant number of workers to be at risk.

GENETIC MONITORING AND OSHA STANDARDS

Some OSHA health standards regulate employee exposure to substances identified as mutagens or clastogens, such as vinyl chloride and arsenic. Since genetic monitoring potentially could identify such substances, could this technique be relied on or required by OSHA in the regulatory process?

OSHA might use the technique to provide data about the harmfulness of a particular substance. If the technique could be used to indicate that a substance was a mutagen or clastogen, data from studies using genetic monitoring could be considered with other evidence when OSHA was setting a standard for a particular substance.

If the technique were sufficiently predictive as a biological dosimeter or as a way to identify a group of workers at increased risk, OSHA might require its use as part of a standard governing a hazardous substance. In that situation, OSHA might rely on the D.C. Circuit Court's decision in the lead standard case, which upheld OSHA's authority to attempt to prevent the subclinical effects of lead disease (38,67).

OSHA REGULATION OF EMPLOYER MEDICAL PROCEDURES

Section 6(b)(7) of the OSH Act gives the Secretary of Labor authority to prescribe the type and frequency of medical examinations or other tests to determine the adverse health effects from exposure to toxic substances. OSHA's 21 health standards regulating toxic substances require a variety of medical procedures. In general, employers must conduct preplacement examinations. The physician must furnish employers with a copy of a statement of suitability for employment in the regulated area, must conduct periodic (usually annual) examinations, and in some instances must conduct examinations at termination of employment

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*101 S.Ct. 2478 (1981).

**448 U.S. 607 (1980).

*According to Assistant Secretary of Labor Thorne G. Auchter, every new standard must now meet four requirements: 1) it must be addressed to a hazard presenting a significant risk to workers; 2) it must be demonstrated that the standard will reduce the risk; 3) the standard must be technologically and economically feasible on an industrywide basis; and 4) the standard must be the most efficient, or cost-effective, way to protect workers (15,61).

OSHA standards for 13 carcinogens require company doctors to take a complete medical history of exposed employees and consider genetic factors.* According to an OSHA directive, however, this does not require genetic testing of any employee and does not require the exclusion of otherwise qualified employees from jobs on the basis of genetic testing (50).

In general, OSHA has not become involved in regulating the procedures and criteria by which physicians make their determinations of the medical fitness of employees. One notable exception concerns the "multiple physician review" procedure, in which employees can select their own physician if they disagree with the findings of the company physicians. The Fifth Circuit Court of Appeals struck down this provision in the commercial diving standard, which required medical examination of employees who were to be exposed to hyperbaric conditions (65). On the other hand, the Court of Appeals for the District of Columbia Circuit upheld such a provision in the lead standard (38,67). The distinction between the two cases appears to be that the provision in the lead standard was shown to be related to a safe or healthy workplace while that in the diving standard was seen primarily as a job security provision and therefore outside the scope of the act. Thus, OSHA probably could regulate genetic testing to the extent the regulations were related to enhancing workplace health.

MEDICAL REMOVAL PROTECTION AND RATE RETENTION

In general, OSHA standards do not indicate what measures an employer may or must take when an employee or applicant is medically unfit for assignment or continued work in an area where there is exposure to toxic substances. In fact, the OSH Act has little applicability to job applicants. Its provisions continually refer to employees but do not refer to applicants for employment, and the term "employee" is not defined in the definitions section of the act to include applicants. Thus, unless prohibited by a collective bargaining agreement or some antidiscrimination law, the employer would be free to refuse to hire an applicant or to discharge an employee based on the employer's determination of medical fitness.

OSHA's only attempt to regulate the effects of medical examinations on employment involves medical removal protection (MRP) and rate retention (RR) of employees previously exposed to certain toxic substances. When a periodic medical examination indicates that the employee is showing symptoms of the adverse effects of exposure, the employee is removed from further exposure —to a "safe" job if there is an opening—until it is medically advisable for the employee to return. If the new position is at a lower rate of pay or if a safe job is not available, RR would require the maintenance of wage and benefit levels during the period of medical removal. Thus, MRP and RR attempt to protect employee health without reducing employee benefits, thereby shifting the economic burden to the employer and ultimately to the consumer.

MRP and RR provisions in OSHA health standards have become increasingly stringent. For example, the vinyl chloride standard provides for MRP, but not RR;* the asbestos standard provides for MRP of employees for whom respirators are ineffective, but RR is required only if there is an available position.** The most sweeping MRP and RR provision is in the lead standard.*** Employees with blood-lead levels above the specified limit must be removed until the level has returned to an acceptable limit. Removed employees retain their earnings rate, seniority, and benefits for up to 18 months.

OSHA's authority to require MRP and RR was called into question by the Supreme Court's decision in the *Cotton Dust* case. Although the Court did not decide the issue of whether OSHA has the statutory authority to promulgate any regulation containing MRP and RR, the Court held that "the Act in no way authorizes OSHA to repair general unfairness to employees that is unrelated to achievement of health and safety goals . . . ."* Because OSHA had not made a finding when promulgating the cotton dust standard that MRP and RR were related to achieving health, the Court struck down that provision of the standard and remanded it to the Secretary of Labor for further consideration.

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*29 C.F.R. §1910.1003 - 1910.1016.

*29 C.F.R. §1910.1017(k)(5) (1981).

**29 C.F.R. §1910.1001(d)(2)(iv)(c) (1981).

***29 C.F.R. §1910.1025(k) (1981).

ACCESS TO EXPOSURE AND MEDICAL RECORDS

Section 8(c)(3) of the OSH Act directs the Secretary of Labor to issue regulations requiring employers "to maintain accurate records of employee exposures to potentially toxic materials or harmful physical agents which are required to be monitored or measured under section 6." On May 23, 1980, OSHA promulgated the rule granting employees a right of access to exposure and medical records.**

Under the rule, any current or former employee or an employee being assigned or transferred to work where there will be exposure to toxic substances or harmful physical agents has a right of access to four kinds of exposure records: environmental monitoring results, biological monitoring results, material safety data sheets, and any other record disclosing the identity of a toxic substance or harmful physical agent. The employee may designate a representative to exercise his or her rights, and labor unions have a right of access to employee exposure records without individual employee consent. OSHA also has a right of access to exposure records. On July 13, 1982, OSHA proposed revisions to the rule, which would narrow its scope significantly.***

Access to employee medical records is more restricted. Employees have a right of access to their entire medical files regardless of how the information was generated or is maintained. The definition of employee does not include job applicants.* A limited discretion is also given physicians to deny access where there is a specific diagnosis of a terminal illness or a psychiatric condition. Unions must obtain specific written consent before gaining access to employee medical records. OSHA has a right of access to employee medical records, but those records in a personally identifiable form are subject to detailed procedures and protections.

Title VII of the Civil Rights Act of 1964

Title VII of the Civil Rights Act of 1964, as amended,** prohibits discrimination in the hiring, discharge, compensation, or other terms, conditions, or privileges of employment because of an individual's race, color, religion, sex, or national origin.

Aggrieved individuals must file a charge with the Equal Employment Opportunity Commission (EEOC) within 180 days of the alleged discriminatory act. After a period of up to 180 days for investigation and conciliation by EEOC, the charging party may file an action in Federal district court.

The term "discrimination" is not defined in title VII, but one court defined it as "a failure to treat all persons equally where no reasonable distinction can be found between those favored and those not favored" (6). The Supreme Court has recognized two main forms of employment discrimination, "disparate treatment" and "disparate impact." Disparate treatment occurs when an employer simply treats some people less favorably than others because of their race, color, religion, sex, or national origin. Proof of discriminatory motive is required. Disparate impact involves employment practices that appear to be neutral in their treatment of different groups but in fact affect one group more severely and cannot be justified by the requirements of the job or business. Proof of discriminatory motive is not required.

The disparate impact concept was established by the Supreme Court in *Griggs* v. *Duke Power Co.**** A unanimous Court struck down the employer's use of certain standardized tests because they disqualified black applicants at a substantially higher rate than white applicants and were not shown to measure job capability.

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*101 S.Ct. at 2506.

**45 Fed. Reg. 35,212 (1980), codified at 29 C.F.R. §1910.20 (1981).

***47 Fed. Reg. 30,420 (1982).

*45 Fed. Reg. at 35,261.

**42 U.S.C. §2000e (1976 & Supp. II 1978).

***401 U.S. 424 (1971).

In *Albemarle Paper Co.* v. *Moody,** the Court clarified *Griggs* and held that a plaintiff may establish a prima facie case of disparate impact by showing that "the tests in question select applicants for hire or promotion in a racial pattern significantly different from that of the pool of applicants." The burden is then on the employer to show that "any given requirement [has] . . . a manifest relationship to the employment in question." The plaintiff may still rebut this evidence, however, by demonstrating that "other tests or selection devices, without a similarly undesirable racial effect, would also serve the employer's legitimate interest in efficient and trustworthy workmanship."

A crucial but still unresolved issue is how different the comparative test results must be in order to support a finding that there was a disparate impact. Most Supreme Court and lower court decisions have considered disparate impact on an ad hoc basis. According to EEOC guidelines on employee selection procedures, "[a] selection rate for any racial, ethnic or sex group which is less than four-fifths (4/5) (or eighty percent) of the rate for the group with the highest rate will generally be regarded . . . as evidence of adverse impact."** This formula is not binding on the courts.

DISPARATE IMPACT OF GENETIC TESTING

The frequencies of genetic traits in the population often vary along racial or ethnic lines. Some examples of these are sickle cell trait, G-6-PD deficiency, and thalassemia trait. According to one study of G-6-PD-deficient individuals (10), the population frequencies for the trait are as follows:

Americans (whites)	0.1 percent
Americans (black males)	16 percent
British	0.1 percent
Chinese	2-5 percent
European Jews	1 percent
Filipinos	12-13 percent
Greek	1-2 percent
Indians (Asian)	0.3 percent
Mediterranean Jews	11 percent
Scandanavians	1-8 percent

Comparing these percentages to each other rather than to the population categories indicates that the use of G-6-PD screening would have a disparate impact on various groups based on race, sex, and national origin. For example, if 1,000 British and 1,000 Filipinos were screened, only 1 British person but 120 to 130 Filipinos would be expected to show a G-6-PD deficiency. Similarly, it has been estimated that 1 out of 12 blacks has sickle cell trait, but only 1 out of 1,000 whites has it, a ratio of 83 to 1.

For title VII purposes, the use of G-6-PD or sickle cell trait screening (or other procedures with a disparate impact) would establish a prima facie case of discrimination. This does not necessarily mean there is a violation, but only that the burden now is placed on the employer to justify the use of the tests.

If future study should reveal that genetic monitoring has a disparate impact by race, a similar legal analysis would apply.

BUSINESS NECESSITY AND JOB RELATEDNESS

In discussing employer defenses in *Griggs,* the Supreme Court indicated that "[t]he touchstone is business necessity. If an employment practice which operates to exclude Negroes cannot be shown to be related to job performance, the practice is prohibited."* Based on *Griggs,* two intertwined defenses have emerged, "business necessity" and "job relatedness." Although the *Griggs* opinion used the terms in the same sentence and did not differentiate between them, subsequent decisions have attempted to do so. Business necessity applies when a general employment practice is used, the purpose of which is not to determine whether an applicant or employee is capable of performing the job requirements. For example, an employer would attempt to use a business necessity defense to justify not hiring someone who had been convicted of a crime.

Job relatedness is somewhat narrower and goes to whether the criteria used in determining whether an applicant or employee is qualified for employment bears a reasonable relationship to the demands of the job. For example, height and weight requirements and passing scores on standardized tests would be evaluated under job relatedness.

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*422 U.S. 405 (1975).

**29 C.F.R. §1607.4 (1981).

*401 U.S. at 431.

The standards used for determining the merits of the business necessity and job relatedness defenses are similar. The key to business necessity is:

> . . . whether there exists an overriding legitimate business purpose such that the practice is necessary to the safe and efficient operation of the business. Thus the business purpose must be sufficiently compelling to override any racial impact, the challenged practice must effectively carry out the business purpose it is alleged to serve, and there must be available no acceptable alternative policies or practices which would better accomplish the business purpose advanced, or accomplish it equally well with a lesser differential racial impact (57).

Once the employer presents evidence to show that its employment practice is grounded on business necessity, the courts balance all the relevant factors to determine whether the need for the practice sufficiently outweighs any disparate impact. In the case of genetic testing, whether avoiding tort liability or costly engineering controls would be a business necessity is an open question.

Job relatedness essentially involves an analysis of an applicant's qualifications and a comparison of legitimate job requirements with the employer's method for determining fitness. In *Albemarle Paper Co.* v. *Moody,** the Supreme Court cited with approval EEOC's Uniform Guidelines on Employee Selection Procedures and held that "discriminatory tests are impermissible unless shown, by professionally acceptable methods, to be 'predictive of or significantly correlated with important elements of work behavior which comprise or are relevant to the job or jobs for which candidates are being evaluated.' " However, the EEOC guidelines have been criticized and the Supreme Court has refused to follow portions of them, particularly when the agency has changed its position on an issue (40). Whether a risk of illness is a job-related characteristic is an open question.

Any distinction between the defenses of business necessity and job relatedness becomes virtually obscured in the context of genetic screening of workers and applicants. An employer's justification for using screening procedures would necessarily involve elements of both defenses. If a suit were to be filed, arguably a court could require an employer's defense to include proof that: 1) there is a valid reason for excluding workers who are presently capable of performing the required work but who may become physically unable or impaired at some point in the future; 2) it is important to the business that employees not be suffering from an occupational illness; 3) the specific screening procedure used accurately and reliably identifies the presence of the genetic trait; 4) there is a high correlation between the trait and the individual's susceptibility to disease at the permissible exposure level; 5) the company cannot feasibly reduce exposure through engineering controls, personal protection devices, or job placement; and 6) the company cannot insure itself at a reasonable cost against potential tort liability.

EMPLOYEE REFUSAL TO SUBMIT TO MEDICAL TESTS

Does an applicant or employee have the right to refuse to submit to a medical test where the employer's use of the results would violate title VII? From an employee standpoint, section 704(a) of title VII offers the best chance of success. This section provides that an employer may not retaliate against an employee or applicant who opposed any employment practice made unlawful by title VII or who participated in any proceeding under the title. Most of the cases brought under this section involve alleged employer retaliation after the employee files a charge with EEOC. Nevertheless, there are some cases holding that other forms of employee activity are protected when they oppose discriminatory employment actions (3,48).

No court has ever resolved the question of whether section 704(a) protects an employee who refuses to submit to a test that he or she believes is discriminatory (and that cannot be justified by the employer). In the one case where the issue was raised, the case was decided on other grounds (43). It is clear, however, that an employee need not be correct; only a good faith belief is required (42,51).

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*422 U.S. 405 (1975).

Based on these considerations, it is possible that an applicant or employee validly could refuse to submit to genetic testing and any retaliation by the employer would violate title VII.

The Rehabilitation Act and State fair employment laws

The Rehabilitation Act of 1973* was the first comprehensive Federal effort to bring handicapped individuals within the mainstream of American life. Of the several provisions of the act, sections 503 and 504 have a direct bearing on the employment rights of the handicapped.

Largely as a result of the Federal initiative, 41 States and the District of Columbia also have enacted laws prohibiting discrimination in employment on the basis of handicap. Unlike the Federal law, which applies only to Federal contractors and recipients of Federal funds, State laws prohibiting employment discrimination against the handicapped have a wider coverage and usually exempt only small employers. Therefore, State law is much more important in cases involving the handicapped than in other kinds of discrimination cases.

Section 503 provides that any contract in excess of $2,500 entered into with any Federal department or agency shall contain a provision requiring that the contracting party take affirmative action to employ and promote qualified handicapped individuals. The term "handicapped individual" is defined as "any person who (A) has a physical or mental impairment which substantially limits one or more of such person's major life activities, (B) has a record of such an impairment, or (C) is regarded as having such an impairment." Based on this broad statutory definition, and on the definition contained in the implementing regulations, it has been estimated that as many as 40 million to 68 million persons are covered by the statute (47). Responsibility for enforcing section 503 is vested in the Office of Federal Contract Compliance Programs (OFCCP) in the Department of Labor. Individuals who believe they have been discriminated against must pursue their remedies through OFCCP; the courts have not permitted these individuals to sue directly.

Section 504 provides that no otherwise qualified handicapped individual shall, solely by reason of handicap, be excluded from the participation in, be denied the benefits of, or be subjected to discrimination under any program or activity receiving Federal financial assistance. Unlike section 503, no minimum amount of financial assistance is required for coverage under section 504, and the courts have held that aggrieved individuals can sue employers under this section. Section 504 also incorporates the same broad statutory definition of handicap as section 503.

Two key terms in the definition of handicapped individual—"physical or mental impairment" and "substantially limits"—are not defined in the statute. However, regulations promulgated pursuant to sections 503 and 504 offer guidance. The regulations under 503 state that a handicapped person is "substantially limited" if "he or she is likely to experience difficulty in securing, retaining or advancing in employment because of a handicap."* The regulations under section 504 define "physical or mental impairment" as:

> . . . (A) any physiological disorder or condition, cosmetic disfigurement, or anatomical loss affecting one or more of the following body systems: neurological; musculoskeletal; special sense organs; respiratory, including speech organs; cardiovascular; reproductive, digestive, genito-urinary; hemic and lymphatic; skin; and endocrine; or (B) any mental or psychological disorder, such as mental retardation, organic brain syndrome, emotional or mental illness, and specific learning disabilities.**

It has been estimated that 3 million firms—about half the businesses in the country—are covered by the act, either as Government contractors or recipients of Federal funds (63).

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*29 U.S.C. §§701-796 (1976 & Supp. III 1979).

*41 C.F.R. §60-741.2 (1981).

**45 C.F.R. §84.3 (j)(2)(i) (1981).

MEDICAL EXAMINATIONS AND SCREENING TESTS

Under the guidelines and model regulations promulgated to implement section 504, an employer receiving Federal financial assistance may not make preemployment inquiry about whether the applicant is handicapped or about the nature and severity of an existing handicap unless a preemployment medical examination is required of all applicants and the information obtained from the examination is relevant to the applicant's ability to perform job-related functions.

Under the section 503 regulations, a Federal contractor may require a preemployment medical examination of a handicapped applicant, even if an examination is not required of the nonhandicapped. Nevertheless, if the employer's job qualification requirements "tend to screen out qualified handicapped individuals, the requirements shall be related to the specific job or jobs for which the individual is being considered and shall be consistent with business necessity and the safe performance of the job."*

Despite the slight difference in language and approach between the section 503 and 504 regulations, both serve to limit the use of discriminatory preemployment examinations and tests. Nevertheless, it still must be determined whether genetic differentiation is a handicap and whether the screening procedures are job related.

IS GENETIC SUSCEPTIBILITY OR CHROMOSOMAL ABNORMALITY A HANDICAP?

The definition of "handicapped individual" basically includes persons who are, were, or are believed to be suffering from an impairment. The goal of genetic testing is to identify individuals or groups who are not at present impaired, but who may be or are likely to become impaired in the future under special circumstances. An important threshold question is whether these individuals are handicapped and thereby protected by the Rehabilitation Act.

In *OFCCP* v. *E. E. Black Ltd.* (17), a carpenter's apprentice was required to submit to a preemployment medical examination which revealed a lower back anomaly known as sacralization of the transitional vertebra. This is a congenital condition found in 8 to 9 percent of the population. Although the disabling long-term effects of the condition are in dispute in the medical profession, the employer conceded that the condition did not affect the applicant's current capability to perform the duties of a carpenter's apprentice. Nevertheless, relying on its medical officer's conclusions, the company determined that the applicant's spinal formation made him a poor risk for later development of back problems and denied him employment. The apprentice filed a complaint with OFCCP, charging the employer with violating section 503.

The Labor Department found in favor of the carpenter's apprentice and ruled that the company's use of preemployment medical examinations tended to disqualify handicapped applicants despite their current capability to perform the job. The Labor Department refused to limit the definition of "impairment" to permanent disabilities such as blindness or deafness. Instead, impairment was held to be "any condition which weakens, restricts or otherwise damages an individual's health or physical or mental activity," resulting in "a current bar to employment of one's choice with a Federal contractor which the individual is currently capable of performing."

On judicial review, the U. S. District Court for the District of Hawaii agreed with the Labor Department that the Rehabilitation Act's coverage was intended to be broad, but it held that the interpretation in the Assistant Secretary of Labor's opinion in *Black* was overly broad (23).* The court pointed out that under the Assistant Secretary's definition of "handicap":

> . . . a worker who was offered a particular job by a company at all of its plants but one, but was denied employment at that plant because of the

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*41 C.F.R. §60-741.6 (c)(2) (1980).

*The court granted partial summary judgment to the Labor Department on two points: 1) the definition of "handicapped individual" contained in the act and regulations is constitutional; and 2) the apprentice was a "qualified handicapped individual" under the act and regulations. On all other issues, summary judgment was denied. In a subsequent decision, the case was remanded to the Department of Labor for a decision on whether the employer met its burden for showing a business necessity defense and for formulation of a standard for the determination of business necessity in this kind of case (22).

> presence of plant matter to which the employee was allergic, would be covered by the Act. An individual with acrophobia who was offered 10 deputy assistant accountant jobs with a particular company, but was disqualified from one job because it was on the 37th floor, would be covered by the Act. An individual with some type of hearing sensitivity who was denied employment at a location with very loud noise, but was offered positions at other locations, would be covered by the Act (p. 1099).

According to the court, the Assistant Secretary's definition ignored critical language in the act that restricts its coverage to handicapped individuals who are "*substantially* limited" in pursuit of a major life activity. Thus, the court held that not every physical condition that limited employment was covered by the act; to be protected, an individual must have been rejected for a position for which he or she was qualified because of an impairment or perceived impairment that constitutes, for the individual, a substantial handicap to employment. The court discussed several factors to be considered in determining whether an impairment substantially limits employability, including the number and types of jobs from which the individual is disqualified, the location or accessibility of similar opportunities, and the individual's own job expectations and training. With respect to the number and type of jobs from which the individual might be disqualified, the court stated that it must be assumed that all similar employers would use the same preemployment examination.

Based on this definition, the court still concluded that the applicant was subject to the protections of the act. First, the applicant's back condition was found to be an impairment or, at least, was regarded as such by the employer. Second, the impairment was found to constitute a substantial handicap to employment because the applicant would have been disqualified from all or substantially all apprenticeship programs in carpentry. Third, the court rejected the employer's contention that Congress did not intend to protect job applicants who have been denied employment based on risk of future injury.

In the context of genetic screening, it may not be that important whether a slight genetic differentiation is in fact a handicap so long as it is perceived to be a handicap by the employer. Both section 503 and section 504 include within the definition of handicap an individual who is "regarded" as having an impairment. Further, on the basis of the *Black* case, a person with a particular genetic trait that is viewed as making him or her susceptible to disease might be found to be handicapped by a court. One factor that the court did not consider in *Black* and that is especially relevant for genetic screening is the consequences of labeling a person with a congenital or genetic anomaly as handicapped, especially since those factors could be handicaps only in certain environments. The adverse psychological impacts of such labeling could outweigh the benefits conferred by the protection of the act.

Most of the cases concerning the definition of a handicapped individual have been tried in State courts under analogous handicapped discrimination laws. The results have varied widely, and it would be difficult to assess whether a given State would be likely to consider genetic differential in itself as a handicap. Nearly all of the reported cases have been decided under the laws of Wisconsin, New York, Washington, and Oregon (40). The Wisconsin and Washington cases have defined the term handicap very broadly. Other State courts, however, have refused to read the statute so broadly, often on the grounds that the legislatures had not intended them to be universal antidiscrimination laws (40).

In New Jersey, a 1981 amendment to the State employment discrimination law* specifically prohibits employment discrimination based on an individual's "atypical hereditary cellular or blood trait." This is defined to include sickle cell trait, hemoglobin C trait, thalessemia trait, Tay-Sachs trait, or cystic fibrosis trait. Thus, New Jersey has become the first jurisdiction expressly to proscribe discriminatory use of some types of genetic screening in the workplace. Florida, North Carolina, and Louisiana prohibit discrimination in employment based on sickle cell trait.

JOB RELATEDNESS OF SCREENING AND MONITORING

Determining that an individual is covered by the act is only the beginning step in analyzing the legality of genetic testing. The Rehabilitation Act protects otherwise qualified handicapped individuals. It still must be decided whether the person is otherwise qualified; if not, the employer would not violate the act by refusing him or her employment.

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*1981 N.J. Sess. Law Serv. 535, 538 (West).

Pursuant to the regulations under the act, a qualified handicapped person is one who can perform the essential functions of the job with reasonable accommodation to his or her handicap.* The regulations under section 503 permit mental or physical screens to the extent they are job related and are consistent with business necessity and the safe performance of the job.** The regulations under section 504 permit such screens only to the extent they are job related.*** Thus, the questions become whether genetic screening is job related or consistent with business necessity and safety and, if so, whether genetic susceptibility can be reasonably accommodated. This section addresses the first question and the next addresses the second.

The Labor Department's decision in *Black* conceded that employers could exclude handicapped individuals from jobs on the basis of legitimate job requirements, but it held that only an individual's current capability to perform could be the subject of inquiry in preemployment medical examinations. The district court termed this interpretation "clearly contrary to law." The court posed the situation where, if a particular person were given a job, he or she would have a 90 percent chance of suffering a heart attack within 1 month:

> A job requirement that screened out such an individual would be consistent both with business necessity and the safe performance of the job. Yet, it could be argued that the individual had a current capacity to perform the job, and thus was a qualified handicapped individual.****

However, the court did not formulate its own legal standard for the circumstances under which possible future injury can be the basis of denying employment.

In *Black,* the court based its determination on its reading of the OFCCP regulation that permitted screens that were consistent with business necessity and safe performance of the job. The comparable regulation under section 504, however, refers only to job relatedness. Thus, a discrimination case based on genetic screening brought under 504 could have a different outcome, depending on how job relatedness is defined. If a court were to define it literally, risk of future illness would not appear to be related to job performance. However, if the court were to define it only in a general sense—for example, the *Griggs* case used it as being synonymous with business necessity—then risk of future illness might properly bar someone from employment. Whether the court would look only to the person's current capability to perform the job or would accept a business necessity defense based on the need for job safety is an unresolved question.

The basic principle that a job requirement that screens out qualified handicapped individuals on the basis of possible future injury may be lawful is in agreement with cases decided under State handicapped discrimination laws. However, it is also clear that the burden is on the employer to justify the denial of employment, regardless of whether the problem is viewed as whether the employee is otherwise qualified or whether the employer has made out a business necessity defense.

An employer seeking to justify using a screening procedure that adversely affects handicapped individuals has a difficult burden of proof. As discussed earlier, in *Albemarle Paper Co.* v. *Moody,** the Supreme Court cited with approval EEOC's Uniform Guidelines on Employee Selection Procedures** and held that "discriminatory tests are impermissible unless shown, by professionally acceptable methods, to be 'predictive of or significantly correlated with important elements of work behavior which comprise or are relevant to the job or jobs for which candidates are being evaluated.' "*** For example, in *Black* it was necessary for the employer to prove that: an important part of the job required the lifting of heavy objects, individuals with back problems would not be able to perform the job, and the X-rays of the apprentice's back had a high predictive value in determining the likelihood that the individual would suffer from back problems. A similar analysis would apply to genetic screening.

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*41 C.F.R. §60-741.2 (1981); 45 C.F.R. §84.4 (k) (1981).

**41 C.F.R. §60-741.6(c) (1981).

***45 C.F.R. §84.13(a) (1981).

****F. Supp. at 1104.

*422 U.S. 405 (1975).

**29 C.F.R. Part 1607 (1980).

***422 U.S. at 432, quoting 29 C.F.R. §1607.4(c).

The relationship between job requirements and future risk of injury has been addressed in State handicapped discrimination cases. In a Wisconsin case (18), the employer excluded an epileptic welder based on evidence that 10 to 30 percent of epileptics under medication still will have seizures. The Wisconsin Supreme Court termed this degree of future risk "a mere possibility" and held that the employer's action was illegal. The court stated that in order to justify an exclusionary practice the employer must show that there is a "reasonable probability" that the characteristics of the employee will result in future hazards to the employee or coworkers. No statistical criteria have ever been established for defining "reasonable probability," but the employer's burden would appear to be quite difficult to satisfy.

Similarly, in an Oregon case (33), an applicant for the job of heavy appliance salesperson was rejected on the advice of the company physician because he had suffered a subendocardial infarction 6 years earlier and had subsequently complained of sporadic angina. The Supreme Court of Oregon upheld the Bureau of Labor's ruling that the disqualification was unjustified because the employer failed to show a "high probability" of future risk of heart attack.

In a California case (64), the employer had discharged a truck driver with a congenital, but not disabling, back condition. The court held that a mere possibility that the employee might endanger his health sometime in the future was inadequate justification for the employer's action.

When there is a strong likelihood that a preexisting condition will be aggravated by exposure in the workplace, an employer's exclusionary practice is likely to be upheld. Thus, in a New York case (71), the court upheld an employer's refusal to hire an applicant who was suffering from dermatitis, where the company physician concluded that exposure to the chemical elements in the plant would so exacerbate the dermatitis as to render the applicant unable to perform his duties.

Moreover, employee exclusionary practices are much more likely to be upheld where the employee's health risk could endanger the health or safety of others (40). This has been especially true in cases involving common carriers, such as buses (68).

REASONABLE ACCOMMODATION

Even if an employer can prove that the screening procedure used is job related and highly predictive, the employer still may not be permitted to discharge or refuse to hire the individual if "reasonable accommodation" is possible. Although neither section 503 nor section 504 mentions a duty to accommodate, the regulations under both sections require reasonable accommodations unless it would impose an undue hardship. According to the section 503 regulations, "reasonable accommodation' may include making facilities accessible, job restructuring, part-time or modified work schedules, acquisition or modification of equipment or devices, and similar actions. It is likely, however, that reasonable accommodation to individuals with proven susceptibility to occupational health hazards would be focused on practices such as shift rotation, dividing maximum exposure time, more frequent monitoring and medical surveillance, and the added use of personal protection equipment. It is doubtful that an employer will be required to reduce exposure levels beneath OSHA PELs to accommodate a susceptible handicapped employee. Most State fair employment practice laws do not require reasonable accommodation (40).

Collective bargaining agreements and employment practices

Protected activities of employees

The National Labor Relations Act (NLRA)* grants employees the right to organize into unions and to negotiate with their employer over wages, hours, and conditions of employment. The agreements that result from these negotiations, known as collective bargaining agreements, can create rights and duties between the parties that go beyond those otherwise required by law. Safety and health matters are considered to be conditions of employment and subject to collective bargaining (44).

Although numerous exceptions abound, safety and health concerns traditionally have not been looked on with a sense of urgency by either employers (19) or rank-and-file employees (26).** Moreover, in times of high unemployment and economic recession it may be assumed that employees would give the highest priority to wages, hours, and job security.

A union is under no duty to bargain for specific safety and health provisions. In fact, as long as it acts in good faith, it is not prohibited from making contracts that might have an unfavorable effect on some employees (24). The decision of whether or how best to protect susceptible employees is a policy decision based on various factors, such as the number of employees involved, the nature of the risk, the predictiveness of screening procedures, and the relative strength of the union's bargaining position. A union might be willing to use economic weapons or forego economic gains to obtain a provision prohibiting the employer from using genetic screening on the assumption that some qualified applicants or members otherwise will be excluded. On the other hand, a union might bargain to require the employer to use cytogenetic monitoring on the assumption that these techniques may show dangerously high levels of exposure to certain chemicals. The union could then bargain for lower exposure levels or other methods of worker protection.

Employee access to safety and health information

Union efforts at negotiating on safety and health matters are often complicated by an inability to obtain detailed information about conditions in the workplace. Unions frequently have requested, but have been denied access to, employee medical records and the identities, properties, and health hazards of various chemicals used in the workplace (49). Employers often object to the release of this information, asserting a proprietary interest, undue burden, physician-patient privilege, employee confidentiality, or trade secrecy.

In *Minnesota Mining and Manufacturing Co.** and two companion cases (12,20), the National Labor Relations Board (NLRB) held that unions have a right to obtain individual employee medical records, the generic names of all substances used in the workplace, and other safety and health data. In the *Minnesota* case, NLRB said, "Few matters can be of greater legitimate concern to individuals in the workplace, and thus to the bargaining agent representing them, than exposure to conditions potentially threatening their health, well-being, or their very lives." NLRB rejected the employer's claim of proprietary interest as irrelevant and claim of undue burden as unsubstantiated. With respect to physician-patient privilege and confidentiality, NLRB noted that the union did not request the names of individual employees and that confidentiality would be safeguarded by having physicians interpret and analyze the documents. Moreover, NLRB held that even where supplying the union with statistical or aggregate medical data may result in identification of some individual employees, the important need for the data outweighs any minimal intrusion on employee privacy. Finally, as to trade secrets,* NLRB ordered the parties to bargain about conditions of disclosure, but, if necessary, the board would strike the balance between the competing claims of the parties.

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*29 U.S.C. §§151-168 (1976).

**The study found that "a little more safety and health" was well behind other job improvements, such as increased retirement benefits, more medical insurance, more paid vacations, shorter workweek, greater chance for promotion, and greater job security, as employment conditions for which workers would be willing to forego a 10 percent pay raise (26).

*261 N.L.R.B. No. 2 (1982).

Provisions in collective bargaining agreements

Safety and health provisions have been included in collective bargaining agreements for many years, but the passage of the OSH Act in 1970 served to promote greater awareness of workplace hazards and increase the importance attached to safety and health in union contracts (25). Some commentators believe that the collective bargaining process offers great hope in fostering the improvement of workplace safety and health (5). However, it should be noted that only about 20 percent of all workers belong to unions.

Numerous safety and health matters can be negotiated, ranging from medical removal protection and rate retention to the formation of joint labor-management safety and health committees. According to one study (16), 82 percent of the contracts in the sample** contained occupational safety and health clauses. The subjects most often covered were safety equipment, first aid, medical examinations, accident investigation, employee obligations, hazardous work, and safety committees.

Medical examinations are required in 30 percent of all manufacturing and 28 percent of all nonmanufacturing contracts. Petroleum (86 percent), mining (75 percent), transportation (72 percent), rubber (67 percent), and stone-clay-glass (54 percent) are the industries where these provisions are most often found. Of the collective bargaining agreements in all industries containing provisions for medical examinations, 29 percent require physical exams for newly hired workers, 34 percent require physical exams when employees are rehired or return to work from layoff or leave, and 74 percent require physical exams periodically or at management's request. In 40 percent of these provisions, employees may appeal an unfavorable medical opinion (16).

As a matter of widespread practice, applicants and new employees have limited rights under most collective bargaining agreements. For example, the great majority of contracts allow the employer to place new employees on probation for periods ranging from 1 to 4 months. During this period, the new employees cannot join the union and they can be fired without union involvement. This practice would hamper negotiations for restrictions on preemployment genetic screening. However, unions could legally negotiate on this point because applicants are considered employees under NLRA and thus subject to its benefits (52). Under the act, therefore, unions would have broad authority to negotiate with employers on whether genetic screening could be used and, if so, under what conditions.

Union's duty of fair representation

Although unions have authority to negotiate on genetic testing, are they legally required to do so? It is well settled that a union has a duty, both in its bargaining and its contract enforcement, to serve the interests of all of its members without discrimination toward any. This is known as the duty of fair representation. A breach of this duty will not be established by simple negligence, but requires a showing that the union acted arbitrarily, perfunctorily, or in bad faith (69).

With respect to genetic screening, two questions arise. First, does the duty of fair representation extend to employees who are found to be susceptible to occupational illness on the basis of their genetic constitution? It is clear that, as employees, they are entitled to fair representation. Second, does a union's duty of fair representation extend to job applicants who are refused employment on the basis of genetic screening? The answer to this question is less clear. Applicants are considered "employees" under NLRA (52), and the union would probably have a duty to enforce an existing agreement containing a provision dealing with preemployment genetic screening. However, it is unlikely that the union would have a duty to negotiate a contract with such a provision (29).

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*A trade secret is a formula, pattern, device, or compilation of information that is used in one's business and that provides an opportunity to obtain an advantage over competitors who do not know or use it.

**The sample contained 400 collective bargaining agreements from a cross-section of industries.

Contract enforcement and arbitration

Most collective bargaining agreements contain an express provision for resolving contract disputes through an internal grievance procedure. If a dispute remains unresolved, however, almost all contracts provide that it will be submitted to an arbitrator voluntarily selected by the parties to the contract.

Since each arbitration decision is based on the specific contract involved, the way arbitrators construe medical examination provisions cannot be generalized. Nevertheless, in cases involving discharge or denial of reinstatement to employees with physical disabilities, dismissal will usually be held to be inappropriate unless the evidence indicates that the employee's disability prevents him or her from performing a job or exposes the employee or other employees to a serious risk of physical harm or injury (74). Even in cases where continued exposure may be injurious to the worker, arbitrators have been willing to allow employees to decide whether to continue work to as long as they are able to and create no risks to others.

Conclusion

Genetic testing raises legal questions related to workplace safety and employee rights. The common law, State workers' compensation statutes, and the OSH Act outline the rights and duties of employers and employees with respect to safety. Title VII of the Civil Rights Act of 1964, the Rehabilitation Act of 1973, and State fair employment practice laws govern rights and duties with respect to hiring, firing, and conditions of employment. Although these statutes and the court cases interpreting them by and large have not dealt with genetic testing, they provide legal principles that are directly applicable to the issues raised by this technology. The principles can provide guidance and some answers to the questions at hand; however, many important questions remain unresolved. In such a situation, the collective bargaining agreements authorized by NLRA could provide a means for employers and unions to negotiate mutually agreeable solutions to the problems raised by genetic testing.

With respect to safety in general, it is clear that the common law and the OSH Act place the responsibility for workplace safety on the employer. Failure to meet the responsibility can result in workers' compensation payments, damages assessed against the employer for tort liability, or civil or criminal penalties against the employer.

This responsibility would not require the employer to use genetic testing, even if it were highly predictive of future illness. If the employer chose to use a highly predictive test, it would likely be negligent if it ignored the results of screening and placed the employee in a high-risk rather than a low-risk environment. However, recovery of damages by such an employee who developed the predicted illness would probably be barred by the "exclusive remedy" provision of workers' compensation laws and possibly by the doctrine of assumption of the risk, if the employee had been informed of the risk. If the risk had been concealed from the employee, recovery would probably not be barred under workers' compensation laws, and the employer would face the possibility of punitive damages.

Under the OSH Act, the Secretary of Labor is empowered to promulgate standards that protect all employees from toxic substances to the extent that the standards are directed toward a significant risk of material health impairment and to the extent that they are technologically and economically feasible. These standards can, among other things, set maximum exposure levels, require personal protection gear, and mandate various medical procedures. The feasibility requirement may leave some percentage of exposed workers at risk, depending on the circumstances of the particular hazardous substance and industry. Of those workers at risk, some may be genetically susceptible and others may be at increased risk because of genetic damage. An open question is whether the courts would allow a standard designed to protect a very small number of susceptible individuals or would invalidate it on the grounds that it failed to address a significant risk because of the small number of workers involved.

The OSH Act and regulations thereunder neither prohibit nor require genetic testing. However, the Secretary of Labor has broad authority to regulate employer medical procedures as long as the regulation is related to worker health and meets the feasibility and significant risk requirements. Therefore, the Secretary could require genetic testing in its various forms, if the techniques were shown to be reliable and reasonably predictive of future illness. The Secretary also could regulate the use of genetic testing, but only to the extent that the regulation was related to employee health. The act grants no authority over rights or conditions of employement per se and no authority to protect applicants for employment from discrimination.

State and Federal law places few restrictions on either the way medical exams or testing procedures must be conducted in the workplace or what the employer does with the resulting information other than the requirements that the procedure not be negligently performed and that the employee be informed of potentially serious health risks. Participation in medical exams or medical research can be a valid condition of employment. As a result, employees or applicants would have no right to refuse to participate without jeopardizing their job. How much the employee needs to be told about the research is unclear, except in two cases. If the research were federally funded, subjects must understand the risks and other aspects of the study and consent to them. A few States have statutes that require Institutional Review Boards in order to protect research subjects, and these boards may require informed consent.

With respect to the data generated by genetic testing, there are few requirements regarding confidentiality except in the State of California. But employees have a right of access to medical records under OSHA regulations and unions have a similar right under a recent decision by NLRB. This access could help prevent abuse of genetic testing. However, those who face the greatest risk of being denied employment because of their genetic makeup—job applicants—would not have access to the test results.

For those applicants or employees who were subject to some adverse job action because of their genetic makeup, Federal and State antidiscrimination statutes may offer some relief, depending on the circumstances of the case. A few States prohibit employment discrimination based on certain genetic traits, usually sickle cell trait. To the extent that genetic screening has a disparate effect on the employment opportunities of one of the protected classes under title VII, an adversely affected genetically susceptible employee in one of those classes would have a prima facie case of discrimination against the employer. The employer would then have to carry the heavy burden of justifying the screening program on the basis of job relatedness or business necessity. It is presently unclear whether avoiding tort liability or the cost of engineering controls is a business necessity or whether the employee's capacity to perform the job without a risk of future illness is a job-related characteristic. However, it is clear that any job selection method must be predictive of the characteristic for which it allegedly selects. Since genetic screening has not been shown to be predictive of future occupational illness, a program that had a disparate impact on the employment opportunities of the classes protected by title VII probably would violate that act.

The Rehabilitation Act and similar State laws offer greater potential than title VII for aiding the employment opportunities of genetically susceptible individuals; however, for those laws to be applicable, two currently unresolved legal questions must be settled in favor of the employees. The first is whether or not genetic makeup is a handicap. If not, these employees would have no rights under these laws. If it is a handicap, the next question is whether a reasonable probability of future illness would be a valid job-related requirement or something going to the necessity of the business. Some State courts have ruled that employment may be denied to handicapped individuals on the basis of a reasonable probability of future illness. If the courts were to rule that future risk of illness was not a legitimate area of inquiry for employers, the Rehabilitation Act and similar statutes would prohibit adverse job actions on the basis of genetic makeup. If risk of illness were recognized as a legitimate concern, the employer would have the burden of showing that the genetic screening techniques were reasonably predictive of illness. Even if the employer demonstrated this, however, it might have to accommodate the "genetically handicapped" employee anyway. Such accommodation probably would not require the installation of expensive engineering controls. In addition to these unresolved questions, a limitation on the Rehabilitation Act from the plaintiff's perspective is that plaintiffs must pursue their remedies under section 503 through OFCCP rather than suing employers directly.

Virtually all of these questions could be subjects of bargaining between employers and unions. Thus, individual employers and unions could decide for themselves whether the employer could use genetic testing, the circumstances under which it could, and the use that could be made of the results. Unions, however, would have no legal duty to bargain over such issues or to take special steps to protect workers who were genetically predisposed to occupational disease.

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Chapter 9

Application of Ethical Principles to Genetic Testing

The use of genetic testing in the workplace touches on areas of basic concern to most people: opportunity for employment, job security, health, self-esteem, and privacy. Genetic screening may enable workers to have greater control over their health by providing medical information on which to base job site selection and use of personal protection devices. It could be used by management to better match employees to their jobs or to reduce levels of exposure to hazardous substances. It also could be used to exclude or transfer people from jobs and conceivably could result in classes of people being stigmatized. While genetic monitoring might permit employees or management to take preventive health measures, it may simply create unjustified fears of nonexistent hazards. Moreover, both techniques result in the collection of information of an extremely personal nature. Thus, the technology has both risks and benefits, depending on how it is used.

Because genetic testing procedures are relatively new and have not been widely used, there is little direct experience on which to make judgments regarding their use. Nor are there direct legal precedents. Under those circumstances, it is appropriate for policymakers and others involved in decisions concerning genetic testing to look to ethical principles for guidance. These principles can assist decisionmakers in ensuring that the technology is used justly and with the greatest regard for human values.

Ethics is the study of moral principles governing human action. These principles, or general prescriptive judgments, create moral duties that guide action in particular circumstances. Sometimes, however, the principles conflict in their application and provide no clear guidance. Then difficult choices must be made. Such is the case with genetic testing in the workplace.

This technology raises a number of questions that can be put in a framework suitable for ethical analysis:

1. Do employers, occupational health specialists, or society in general have any particular obligations toward workers who may be at increased risk for disease because of their genetic constitution or because of exposure to hazardous substances? If so, what are they?
2. Are genetic screening and monitoring for genetic damage compatible with ethical principles?
3. Does the answer to the second question depend on the particular circumstances involved? If so, the following must be examined:
   a. What moral rights and duties exist between the worker and company medical personnel?
   b Must participation in genetic testing programs be voluntary, and if so, how is that to be guaranteed?
   c. What rights and obligations exist regarding the use of medical information?
   d. What ethically permissible actions may be taken on the basis of information gained through genetic testing programs?
   e. Do the answers to these questions depend on whether the testing is being done for research purposes or as part of a medical program?

To address these questions, it is first necessary to consider some basic ethical principles. Their application to the various ethical questions raised by genetic testing then will be discussed.

Ethical principles

Four ethical principles are most relevant to an assessment of this technology: autonomy, nonmaleficence, beneficence, and justice.

Autonomy

The principle of autonomy has two aspects. The first relates to the ability of a person to make considered judgments and decisions that lead to acts that foster self-reliance or independence. In this sense, autonomy depends on being able to plan and act deliberately, based on one's own judgment about the consequences of certain behaviors and their value or utility to oneself or others. This leads to the notion that individuals should be free to act as they wish, regardless of how foolish their actions may appear to be and without interference by others, so long as their actions do not harm others or interfere with their liberty (2). The second aspect of autonomy derives from the belief that people should be treated as ends rather than means, a principle known as respect for persons. In other words, in evaluating the actions of others, one should respect them as persons with the same right to their judgments as one has to his or her own (2). Thus, the principle of autonomy imposes the dual moral obligation not to interfere with the autonomous actions of others and to respect their personhood and beliefs.

A corollary of the principle of autonomy is the requirement to secure informed consent from persons before taking actions that may put them at risk. The rule of informed consent requires full disclosure of all important information, comprehension of the information, the ability to choose freely, and the mental competence to make decisions (7). Thus, the rule serves to protect individual autonomy.

Not everyone is capable of full self-determination. This capacity develops during a person's life, and some individuals lose it in whole or part because of illness, mental disability, or circumstances that severely restrict their liberty. For example, children, prisoners, or those who are in institutional settings may be less capable of autonomous actions (7).

Autonomy may be compromised in other ways. These include situations where behavioral options are limited, where direct or implied coercion is used toward actions favored by others, or where circumstances limit the ability to act knowledgeably in one's own interest.

Workers as a group may be situated in ways that limit their full expression of autonomy. Preordained rules of behavior, job requirements, limited resources or information, and concern over job security can limit autonomy. Whether or not particular limitations are justified will depend on a determination of the validity of reasons for overriding the principles of autonomy.

Respect for persons gives rise to the obligation to protect those with diminished autonomy (7). The extent of protection generally would depend on the degree to which their autonomy is diminished. Some persons require little protection beyond ensuring that they undertake activities voluntarily and with an awareness of possible adverse consequences; others may have to be excluded from activities that harm them.

The principle of autonomy is not absolute. Where the prospect of severe harm is evident, some commentators have argued that intervening in order to protect the individual is justified (3,6). Thus, it may be justified to intervene where persons are otherwise competent to exercise autonomous thought and action (as is the case for the great majority of workers), but who may be unable to so act because of their ignorance of the risks or their inability to understand those risks due to their complex technological nature.

Genetic testing has the potential to be used in a way that restricts the autonomy of prospective employees or workers already on the job. For instance, preemployment tests that presumably identify genetically susceptible individuals may be used to restrict the type of job an employee is permitted to undertake or to ban the worker from employment in the industry altogether. Similarly, testing done during employment, which detects early warning indicators of possible future disease, might be used preemptively to remove employees from a given station or set of job duties. Each of these steps, if taken unilaterally by an employer, could be seen as a restriction of the autonomy or liberty of the individual worker to elect a suitable job and/or to accept the attendant risks.

Nonmaleficence and beneficence

Nonmaleficence is the obligation not to harm others (2). Beneficence is the obligation to help others further their important and legitimate interests when we can do so at minimal risk to ourselves (2). In practice, it is difficult to separate the two principles, because avoiding harms and producing benefits exist along a continuum. However, one philosopher, William Frankena, separated this continuum into the following duties:

1. One ought not to inflict harm.
2. One ought to prevent harm.
3. One ought to remove harm.
4. One ought to do good.

Frankena stated that each of these duties should take precedence over the next, so that nonmaleficence is the strongest duty, and doing good is the weakest (5). Beneficence is usually considered to encompass the second, third, and fourth elements; it is distinguished from nonmaleficence in that it requires positive steps to help others and not merely restraint from harming them (2).

In a workplace setting, this priority listing could correspond to an employer's duty to: 1) not knowingly subject workers to conditions that are likely to cause injury or ill health, 2) take steps to prevent the likelihood of workers becoming injured or diseased, 3) remove harmful substances, and 4) take affirmative actions to improve worker health.

Our society generally accepts the proposition, as reflected in our legal system, that we cannot legitimately impose an affirmative duty to do good, but may impose negative injunctions to avoid harm. However, in certain cases, usually involving special relationships such as that of employer-employee or doctor-patient, society imposes a duty to prevent or to remove harm. For example, the policy embodied in the Occupational Safety and Health Act of 1970 that all workplaces be safe and healthy can be interpreted as the legal imposition on employers of at least a duty to prevent harm and remove potentially harmful conditions.

Arguments in favor of genetic testing rely on the principles of beneficence. If the tests are able to identify individuals or populations at increased risk, the employer has the duty to prevent harm by preventing exposure to harmful substances or to remove the harm by reducing the level of exposure.

Such action may conflict with the principle of autonomy, however, where it overrides a person's own informed choice. An example would be where a job was denied to a susceptible person who was willing to accept the risk. Whether or not such paternalistic actions are justified depends on whether one places beneficence above autonomy. Generally, ethicists favor autonomy over beneficence (2), a choice also widely reflected in judicial decisions and legislation.

The concept of beneficence embodies the notion of maximizing possible benefits and minimizing possible harms (2). This leads to the requirement for a risk/benefit assessment whenever a technology is claimed to provide benefits, such as prevention of illness. As applied to genetic testing, this would require at a minimum that the claimed benefits in fact exist. In other words, the association between one's genetic makeup and disease or between damage to one's chromosomes or DNA and disease must be scientifically demonstrated.

Justice

Justice is a broad and elusive concept. Different moral philosophers have explained it in terms of freedom, fairness, equality, or entitlement. Most would agree, however, that an injustice occurs when a benefit to which a person is entitled is denied without good reason or when a burden is improperly imposed. A more positive and often quoted statement of the principle of justice is that equals should be treated equally, and unequals should be treated unequally (2). But what does this tautology really mean? Who is equal and who is unequal?

A somewhat more useful formulation of the principle of justice says that individuals who are equal in relevant respects should be treated equally, and individuals who are unequal in relevant respects should be treated differently in proportion to the differences (2). The problem then becomes to determine relevant differences. Most commentators would allow distinctions based on ability, experience, need, and merit to justify differential treatment, depending on the circumstances. In addition, the other moral principles already discussed provide some guidance in determining whether particular differences are relevant (2).

A slightly more restricted notion of justice is the concept of distributive justice, which refers to the proper distribution of social benefits and burdens among different classes of people. There are several widely accepted formulations of just ways to distribute benefits and burdens on the basis of relevant differences. These are: to each person an equal share; to each person according to individual need; to each person according to individual effort; to each person according to societal contribution; and to each person according to merit. These principles may give conflicting results in particular cases (2).

Thus, it is clear that a precise statement of the requirements of the principle of justice is best left to a case-by-case analysis. Its application to genetic testing will be discussed in the context of the particular ethical issues raised in the following section.

Applications to genetic testing

Ethical principles can provide some guidance to policymakers and others who must decide whether or not genetic testing should be done in the workplace and, if so, under what circumstances. This section first considers the routine use of genetic tests for clinical purposes at their current level of development, where there is low correlation between the endpoints and risk of disease. It then considers the use of genetic testing at its current level of development for purposes of medical research. Next, because the technology is developing, it considers the issues raised by the clinical use of these tests, where there is an assumed high correlation between genetic endpoints and risk of disease. Finally, two particular problems that arise in all three of these situations are considered: What should an employee be told about test results? What are the obligations of the employer and company medical personnel to maintain confidentiality of medical data?

Routine use of tests of doubtful clinical value

GENETIC SCREENING

The use of genetic screening to identify individuals who might be at an increased risk of disease in a workplace environment could not be justified by the principle of beneficence where there was a low correlation between the genetic endpoints and disease. There would be great uncertainty over whether or not that individual would be at increased risk of harm. Thus, it would be uncertain whether the employer could prevent harm. At the same time, there would be some risks to the workers. First, there would be some physical risks associated with the medical procedures. Second, there would be risks to the worker from the use of the information. These include adverse job actions, loss of self-esteem, and possible stigmatization from being labeled "genetically inferior." Such a label conceivably could result in the person being barred from certain jobs in an entire industry. In addition, it would be particularly troublesome if placed on historically disadvantaged groups because it could help continue that status. In view of the substantial risks and uncertain benefits, one could not argue that poorly predictive tests could be used to prevent harm.

If the person labeled as susceptible were fired or excluded from a desirable job, such action would not comport with the principle of justice. It would be difficult to argue that genetic makeup was a relevant characteristic for treating one group of workers differently from another, when the scientific data at best show only a weak association between genetic makeup and susceptibility to disease.

GENETIC MONITORING

Under circumstances where there is only a weak association between cytogenetic or noncytogenetic endpoints and disease, the use of genetic monitoring in the course of clinical practice would also raise ethical concerns; however, monitoring may be somewhat less at variance with accepted ethical principles than genetic screening. Arguably, there could be a small benefit to an entire group of people if the tests indicated they might be at an increased risk of disease. Moreover, the risks would be minimal; they include the physical risks of drawing blood and the possibility that some anxiety about future illness would be created unnecessarily. Presumably, there would be less of a risk of adverse job actions than for screening because monitoring cannot identify individuals who might be at increased risk. Assuming the workers were not subject to job discrimination or other adverse action, there would not be problems with respect to the principle of justice.

The strongest ethical argument against such testing, whether screening or monitoring, would be based on autonomy. The concept of respect for persons requires people to be treated as ends, not means. Using medical procedures of questionable value on people could only be justified by the voluntary and informed consent of those subject to the procedure.

Medical research

The use of techniques of low or uncertain clinical value for purposes of research can be ethically justified when certain conditions are met (7). The underlying purpose would be beneficent; if the research showed the techniques to be useful or led to their further development, society would benefit. Those workers participating in the research also might benefit at some future time. The risks to them would be similiar to those discussed previously, except that there would presumably be less of a risk of adverse job actions being taken. However, there would still be the psychological risk of a person gaining information about himself that he might prefer not to know.

Under these circumstances, where participants in medical research are not likely to benefit directly from the medical interventions, the principle of autonomy becomes paramount. This principle usually requires that the subjects enter into the research voluntarily and with adequate information (7). In practice, this means that the subjects must give informed consent to the procedures.

The elements of informed consent are disclosure of information, comprehension of information, and voluntariness (7). Competence to consent is sometimes viewed as an element of informed consent and sometimes as a precondition. In any event, it would not be relevant here because it refers to the mental capacity to make decisions on a rational basis. Workers actually on the job are presumably competent.

The type of information disclosed usually includes the research procedure, its purpose, the risks and possible benefits, the fact that the subjects may ask questions, and the fact that they may withdraw at any time. Generally, the subjects should be told what a "reasonable person" or perhaps a "reasonable volunteer" would want to know about the experiment (7).

Information must be presented in a way that is understandable to potential subjects. Moreover, the investigators are generally considered to have an obligation to determine that the information was understood. (7).

Voluntariness requires conditions free of coercion or undue influence (7). This may be especially problematical in an occupational setting where workers may perceive their job security or potential for promotion to be affected by their willingness to participate in the research.

High correlation between genetic endpoints and risk of disease

GENETIC SCREENING

In the hypothetical case where particular genetic traits correlated with an increased risk of disease, genetic screening could be supported by the principle of beneficence, depending on how the results were used. Clearly, the data generated by the tests would identify a potential harm, and given this information, steps could be taken to prevent the harm or to remove it. How the information is used then becomes the paramount question.

One action that the employer could take would be to bar genetically predisposed workers from certain jobs, by not hiring them, by placing them in other jobs when hired, or by transferring them. This action might be considered beneficent because harm to the employee would be averted. However, another action, also consistent with beneficence, would be to lower exposures to the point where these people would not be at increased risk. Still another action might be to devise personal protective equipment for them. The principle of beneficence provides little guidance in choosing among these alternatives.

The principle of justice provides some guidance. One way of considering the problem would be to ask if genetic makeup is a relevant characteristic on which to treat a small part of the work force differently. One could argue that genetic makeup is relevant because, in our hypothetical case, these people are more prone to illness. This illness would result in additional costs to themselves, the employer, and society. It may be unfair for society or the employer to bear these costs for the benefit of these few individuals. On the other hand, these people are not responsible for their genetic makeup. Therefore, it is arguably unfair to single them out for special treatment. In addition, their genetic makeup may be irrelevant because it is not related to their ability to do the job efficiently and without risk to others.

Another way to address the problem is to ask who, if anyone, has the obligation to compensate genetically disadvantaged workers? Three schools of thought on distributive justice are relevant: the libertarian school; the utilitarian school; and the needs-based school.

The libertarian school emphasizes merit and contribution. Under this theory, a worker or group is entitled to get back exactly that proportion of the national wealth that he or they created (4). If genetically disadvantaged workers were not contributing to the national wealth, even if the reason was because they had been denied jobs, they would not be entitled to compensation, according to this school.

The utilitarian school emphasizes consideration of all of the various principles of distributive justice with the goal of maximizing public and private benefits (2). Under this theory, one could argue that compensation could materially help these individuals at little cost to society, which would bear the costs directly through government compensation plans or indirectly, when the employer passed on the costs in the price of the product. On the other hand, if the costs of compensation were large and the number of workers were small or if employers were forced out of business by having to install extremely expensive engineering controls, one could argue against compensation.

The needs-based school emphasizes fundamental needs; that is, something without which a person will be harmed or at least detrimentally affected. If genetically disadvantaged workers faced at least moderate difficulty in finding any job or a job at an adequate wage level, this theory would require compensation.

The principle of autonomy is also important in this hypothetical situation. Respect for persons would probably require that genetically susceptible workers be informed of their condition. At the same time, autonomy would appear to require that such workers be given the right voluntarily to assume the risk, if given adequate information in a comprehensible way. In situations of conflict between autonomy and beneficence, most ethicists generally favor choosing autonomy. Thus, paternalistic behavior on the part of the employer to exclude the employee for the latter's benefit but without his consent generally would be viewed as unethical. However, society sometimes accepts paternalistic actions when they benefit affected groups, such as compulsory vaccination or fluoridation of the water. If genetically susceptible workers were given alternative jobs at equivalent pay and benefits, the paternalistic behavior of excluding them from certain jobs probably would be ethical.

GENETIC MONITORING

If there were a high correlation between cytogenetic or noncytogenetic endpoints and risk of disease, genetic monitoring could be justified by the principle of beneficence. The reasons would be essentially the same as those discussed for screening.

The actions that an employer may take on the results of monitoring are somewhat different, however. Unless the monitoring tests were so predictive that high-risk individuals could be identified, a situation that would be the same as screening, monitoring would only identify a high-risk group already on the job. The most likely courses of action open to the employer would be to do nothing, to lower exposure levels, or perhaps to take some intermediate action such as providing personal protection devices.

Doing nothing to alleviate a known risk would be unethical. Since the employer actually created the risk, inaction would amount to inflicting harm. Moreover, autonomy would appear to require informing the workers of their increased risk, arising from being members of the group.

Lowering exposure levels or providing protection devices would be consistent with the principle of justice. No discrimination would be involved, and employees would not unfairly bear the burden of the actions.

Special problems

Two problems deserve special attention because they arise regardless of the predictiveness of the various tests: What information should be given to workers about testing procedures and the results? Who besides the employees should have access to medical data and under what circumstances?

The principle of autonomy implies a duty to provide employees with information about their health, even where the significance of the information might be uncertain. This duty would be even stronger when the information was highly predictive of a risk of disease.

Autonomy would also appear to require that workers be fully informed of the nature of medical procedures to which they are subjected. While the concept of informed consent would be most crucial in a medical research situation, it is also applicable to clinical interventions. In the latter case, even though the procedures are clearly beneficent, their application to the worker without his informed consent is a paternalistic action.

Once medical data have been collected, the issue of who has access to the data arises. As a general rule, medical data are considered confidential on the grounds that respect for a person's autonomy requires respect for his or her privacy. The stringency of this rule, however, is a matter of much debate, particularly in the work environment where the employer is viewed as having some rights to that information. The Code of Ethical Conduct for Physicians Providing Occupational Medical Services states that employers are entitled to be informed of the medical fitness of individuals for work but are not entitled to diagnoses or details of a specific nature (1). One potential consequence, however, might be that workers determined to be genetically unfit could be stigmatized and have difficulty finding other employment for similar jobs.

Conclusions

Genetic screening and monitoring are not inherently unethical. The tests are morally justified to the extent they enhance worker health in a manner consistent with the principles of autonomy, nonmaleficence, beneficence, and justice. Whether or not they are consistent with these principles will depend on how the tests are done and how the information is used.

Ethicists generally agree that autonomy requires that no medical procedure, especially those of unestablished clinical validity, be done on a person without his informed consent. This principle would also require that the person be told the results and what they mean and that medical data be held confidential.

Ethical principles constrain how the results of genetic testing may be used. With a low correlation between genetic endpoints and disease, it would be unethical for the employer to act adversely to the employee's interests, such as by denying him or her a job. In the hypothetical case of a high correlation between genetic endpoints and disease, the morally correct course of action is significantly less clear. An employer may be justified in allowing a susceptible person to assume the risks on the basis of informed consent. On the other hand, the most ethically feasible course of action for an employer once genetic monitoring identifies a group at increased risk would be to inform the workers and to reduce workplace exposure. Failure to do so would be inflicting harm, and it is unlikely that the group would consent to assuming this risk. Finally, whether or not genetically susceptible people are entitled to compensation depends on which theory of distributive justice is chosen.

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Chapter 10

Prospects and Problems for the Economic Evaluation of Genetic Testing

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Chapter 10

Prospects and Problems for the Economic Evaluation of Genetic Testing

Introduction

Genetic testing in the workplace has potential benefits and costs to workers, employers, and society as a whole. The magnitude of those benefits and costs and their distribution among the sectors of society will help determine the desirability of this approach to improving occupational health. The techniques of economic evaluation—cost-benefit and cost-effectiveness analyses—are methods for collecting, organizing, and presenting evidence about the benefits and costs of alternative courses of action. They are systematic approaches to examining the tradeoffs among the different kinds of consequences—for example, dollar outlays today versus improved levels of health 5 years hence—stemming from a decision.

The usefulness of economic evaluation rests on its ability to improve decisions. Even when economic analysis is severely limited by uncertainties about the magnitude, direction, or value of certain consequences—as is the case with genetic testing—it can still be a useful exercise. The very identification of key areas of uncertainty, for example, can be used to set priorities for further research. It can also show how sensitive the results of an analysis are to changes in assumptions concerning these uncertain elements of the decision.

This chapter considers the fundamental principles and limitations of economic evaluation and proposes a general framework for economic evaluation. Then, the specific issues and problems that arise in applying the framework to genetic testing are discussed. The goal is to illustrate the kinds of information that are currently available to support such analysis and the present level of knowledge about the costs and benefits of these approaches to occupational health.

Economic evaluation in health

The analytic pillars of economic evaluation are cost-benefit and cost-effectiveness analyses. They share a common purpose—to help decisionmakers understand the consequences of the choices before them. This objective is approached from different perspectives under the two techniques. Consequently, each technique has strengths and limitations that make it more or less acceptable to analysis of particular problems.

General principles

In theory, a cost-benefit analysis identifies, quantifies, and places a value on all consequences, both positive (benefits) and negative (costs) arising from each possible alternative course of action. If all such consequences are valued in the same unit of measure (for example, dollars), the decisionmaker would merely have to tally these values and compare them across all possible alternatives. The alternative with the highest level of net benefit (or lowest net cost) would be preferred to all others.

In practice, no cost-benefit analysis is ever completely comprehensive or accurate in measuring consequences, and the valuation of such consequences, even when they can be measured, is replete with conceptual and methodological difficulties. Consequently, in practice a cost-benefit analysis is not a definitive decisionmaking tool but rather a useful framework for arraying information (11).

Indeed, the Achilles' heel of cost-benefit analysis is its need to assign a monetary value to all measured consequences of each alternative. This value is generally accepted as the sum of the values of the consequence to each affected member of society. But how does one assess the value that a person places on a reduction in the probability of early death, pain, or discomfort associated with illness, especially when the changes may occur at different times in the future? The question of how to value consequences has been addressed at length in the cost-benefit literature (11). Methods do exist (some of which are discussed below) that are generally accepted by economists as reasonable for assigning monetary values to some important consequences. None, however, is completely satisfactory, and the technique of cost-effectiveness analysis was developed to sidestep the valuation problem.

In cost-effectiveness analysis, the monetary costs of an alternative are compared with one or more measures or indexes of effectiveness, such as "number of lives saved," "number of life-years saved," or "quality-adjusted life-years saved" (11,16). The effectiveness measure must act as a surrogate for all of the nonmonetary consequences that are otherwise unmeasured. Only those alternatives whose consequences are well represented by the selected effectiveness measure should be compared with one another. Consequently, cost-effectiveness analysis can be used to compare only a narrow range of alternatives. Whereas cost-benefit analysis is theoretically powerful enough to compare widely different alternatives, such as occupational health programs versus housing programs, cost-effectiveness analysis can be used only to compare alternatives with the same or a very similar range of nonmonetary consequences, such as different approaches to reducing workers' exposure to a particular industrial carcinogen.

Economic evaluation does not require the aggregation of all benefits and costs into a single index. Recently, some scholars have advocated a social accounting approach in which all of the important dimensions of benefit and cost are arrayed and, to the extent possible, their magnitude estimated (11,17). Some dimensions would be measured in dollars, some in physical units, and some in constructed scales. The decisionmaker would have a balance sheet showing the performance of each alternative on each dimension. The advantage of this disaggregated approach is that important but hard-to-measure consequences of an alternative will not be ignored. However, if many dimensions of outcome are important but cannot be measured precisely, the enumeration of effects can obscure rather than clarify the differences among alternatives.

Identifying and measuring consequences

What are the consequences of alternative strategies for achieving occupational health? Such strategies typically reduce exposure to illness- or injury-causing hazards. This exposure reduction presumably lowers the incidence or severity of occupational illness. These positive health effects are bought at the price of the occupational health program expenditures. But the positive health effects of the program also mean reductions in the cost of illness. The cost of illness has three components, each of which may be altered by the program's health effects. First, the reduction in the incidence and severity of illness over workers' lifetimes will mean fewer expected expenditures for health and medical care at various points in the future. The discounted value* of these immediate and future monetary outlays is called the direct cost of illness.

The consequences of a strategy do not end with these direct costs. When a worker dies or falls ill, his or her productivity is lost or diminished. This productive activity has a value in the market place, and its loss is referred to as the indirect cost of illness. Thus, a program that improves worker health will reduce the indirect cost of illness as well. But the consequences of illness go still further. Quite apart from its effect on productivity, illness brings about pain, suffering, anxiety, emotional distress, and grief in patients, their families, friends, and others. The value of these losses are the psychosocial costs of illness (1).

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*An outlay in the future cannot be compared directly with one made today because the postponement of the expenditure allows for the investment of those funds in alternatives and because people prefer a benefit today to one in the future. The value of the future expenditure must therefore be discounted by a rate equal to the return from those alternative investments.

The "benefit" of an occupational health strategy is the value of changes in these costs of illness due to the program. The goal of cost-benefit analysis is to measure the impact of a program or strategy on the cost of illness and to compare this benefit with the cost of the program. If the difference between benefit and cost is positive, society would be better off if it were to implement the strategy. If the net benefit is negative, however, the program is not worth its cost. The assumption underlying these conclusions is that all of the costs and benefits can be quantified.

The challenges to measurement and valuation of the cost of illness are great, even when the health effects of a program are known with precision. There are two different conceptual approaches to measuring the cost of illness: human capital and willingness to pay. Illness is something that people are clearly willing to pay to avoid, and in theory, this willingness to pay is the value of the health benefits resulting from a program. But for a variety of reasons it is not easy to determine how much people would be willing to pay to reduce, say, the probability of contracting a given disease at some point in the future.* Consequently, most cost-benefit analyses employ the human capital approach to valuing benefits.

The human capital approach measures only those benefits that have a value in the market place: the direct and indirect costs of illness. Psychosocial costs are left to be considered in some other way. Under this method, the value of lost production due to illness or death is measured by the market price for workers' labor. Occupational health strategies directed toward those members of society with lower wages or lower rates of participation in the work force, such as women, minorities, and the elderly, therefore would be valued at less than those aimed at others.

Cost-effectiveness analysis typically does not involve the valuation of either the indirect or psychosocial costs of illness. The effectiveness measure (such as life-years saved) presumably acts as a proxy for both of these. The net costs of a program are defined as the sum of the direct program cost and the change in the direct cost of illness—that is, present and future medical care costs. If this net cost is negative, the program is cost-saving without even considering effectiveness. But if program expenditures outweigh the discounted value of savings in direct medical care costs, ratios of net cost to effectiveness then are constructed for each alternative under study.

The cost-effectiveness approach also contains built-in value judgments. For example, the "life-years saved" measure would treat 10 extra years of life to a 45-year-old patient the same as 10 extra years of life to a 70 year old. There is substantial evidence from survey research that the value of these outcomes is not the same in most people's minds (4), but a cost-effectiveness analysis using the life-years measure would not be able to account for such differences.

Problem of value judgments

Biases and value judgments are inherent in all economic evaluations, no matter how comprehensive. Value judgments creep in through the framing of the question, the choice of measures of benefit, effectiveness, and cost, the choice of data sources, and the design of measurement instruments. A value judgment also is present in the general neutrality of economic evaluation toward the winners and losers of a decision. Each alternative will affect the distribution of benefits and costs among segments of the population. These differences generally are netted out in economic evaluations under the assumption that if the winners could more than compensate the losers, society as a whole would be ahead, whether or not the compensation actually takes place.* In reality, of course, such compensation rarely occurs; consequently, economists increasingly have come to view the analysis of distributional consequences of alternatives as a fundamental element of economic evaluation, especially when they are major (17).

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*For a discussion of the willingness-to-pay concept, and the difficulties of measuring it, see ref. 6.

*For a discussion of the compensation test, see ref. 7.

Perhaps the most important value judgment in any economic evaluation is the definition of alternatives. Relevant alternatives can be easily excluded from consideration simply because they are not recognized at the time the study is designed. In genetic testing, the definition of a strategy must include not only the testing protocol and procedures, but also the followup and enforcement activities that follow testing. Minor modifications in the definition of a genetic testing strategy, such as the inclusion or exclusion of counseling services for employees, can have major effects on program costs, anticipated health effects, and psychosocial consequences. Yet, available funds may limit the number of alternative strategies that can be compared, so choices must be made as an analysis is designed. Often, one cannot be certain that the best strategy has been included as an alternative in the study.

Framework for economic evaluation

There are five critical elements of any economic evaluation, be it cost effectiveness, cost benefit, or some hybrid of the two. This section identifies and discusses the five components.

Alternatives compared

The most important characteristic of an evaluation is the set of alternatives chosen for study, since the usefulness of an analysis for any decision depends on the choice of relevant alternatives. There are two entirely different kinds of relevant alternatives for genetic testing in the workplace. The first involves strategies for research on genetic testing, including development and refinement of the testing technology and epidemiological and clinical research on the relationship between occupational exposure and disease in various human populations.

The second set of alternatives involves the use of these tests to screen or monitor specific worker populations with the purpose of following up on the test results with strategies to reduce exposure. These are strategies of intervention, as opposed to research.

It is possible to structure the research question as one for economic evaluation on the rationale that limited research resources should be allocated to projects that can promise the highest ratios of benefit to research cost. But the measurable benefits of research rest largely on the benefits of the interventions subsequently made possible by it. Thus, even economic evaluations of alternative research strategies must consider interventions. To date, the use of economic analysis as a guide for biomedical research has been limited. This is primarily the result of the inherent difficulty of predicting the outcomes of research projects, their timing, and even their probability of occurring. Consequently, the discussion in subsequent sections will concentrate on alternative strategies for implementation of genetic testing.

Population studied

The definition of the population to which the alternatives apply is also an important attribute of any analysis. A comparison of two alternatives can have widely different results depending on the characteristics of the population. For example, the potential importance of age as a factor in susceptibility to exposure argues for separation of populations into age groupings. Narrowly defined populations have an advantage in that the interpersonal variation in measured costs and benefits is low. On the other hand, if the worker population is defined so narrowly that few fall into each category, the analysis may lack the statistical power to identify differences among alternatives even when they actually exist.

The population also may be defined so narrowly that the benefits and costs associated with a strategy cannot be achieved in actual practice. Consider, for example, the costs and benefits of genetic screening for thalassemia trait in workers. If the study were to compare alternatives only for workers in specific high-incidence ethnic or racial groups, the results might be irrelevant for the actual operation of an occupational health program, where it may not be ethical or lawful to require the test on the basis of race or nationality. In other words, an economic analysis might show the desirability of screening for thalassemia trait if the procedure were limited to blacks and Mediterraneans, whereas in reality no screening program could be limited to that population.

The consequences considered

As discussed earlier, an economic evaluation may be characterized by the range of consequences (costs and benefits) included in its purview. It is possible to consider only the direct costs of a program. If, for example, a screening program can be shown to reduce net direct costs (consisting of the sum of the cost of administering the program and the net reduction in the discounted costs of present and future health care), consideration of other consequences, such as the indirect and psychosocial benefits, may be unnecessary. However, a usual precondition to the accurate estimation of the net direct costs of a strategy is the ability to estimate the impact of the program on the health of workers and therefore on their need for medical care. Thus, even ignoring the indirect and psychosocial costs, economic evaluation generally cannot evade the need for some estimate of a strategy's health effects.

Inclusion of indirect cost impacts into an economic assessment adds an additional degree of complexity to the evaluation problem. Even when it is possible to assess the impact of a program on the incidence of disease, it may be difficult to assess its impact on the person's ability to work at his or her level of productivity.

Methods for aggregating consequences

The consequences of any action will be distributed over time and among the members of society. These effects must be aggregated into coherent summary measures if the analysis is to be useful to decisionmakers.

The usual approach for dealing with effects occurring through time is to discount future costs or benefits by an appropriate rate. The further away in the future that a consequence will occur, the less importance or value it will have when discounted. There is no generally accepted "correct" rate at which future consequences should be discounted to their present value. Discount rates of 3, 5, and 10 percent per year are common. Even nonmonetary effectiveness measures such as "lives saved" are often discounted in economic evaluations, though it is difficult to determine the appropriate discount rate for these kinds of effects. Estimates of lifetime direct and indirect costs vary widely with the choice of discount rate (3,6).

Aggregating consequences across individuals also is necessary. Two issues are pertinent to the aggregation methods employed. The first is the statistical issue of the best measure to represent a potential distribution of impacts. Commonly accepted measures such as the mean or median may obscure important effects occurring in a subset of the population. The direct and indirect costs of large changes in health status may be quite different from those of smaller changes, and measures such as the mean may not reflect these important differences.

The second issue is one of equity. Consequences are likely to be differentially distributed among sectors of the society. Exposed workers comprise one affected group, the industrial employer another. Workers in other industries and the general public are other affected sectors. Analyses can be, but rarely have been, structured to show how the costs and benefits of a program are distributed among these groups.

Study design

All analyses ultimately rest on estimates of the expected effect of each alternative on the consequences of interest. How these estimates are derived will determine their validity and, hence, the validity of the economic evaluation itself. Thus, the issues inherent in study design in general—internal and external validity—are important in economic evaluation as well (2).

Most economic evaluations contain one or more estimates that are based on assumptions or rules of thumb. Estimates are often necessary because of a lack of data. When such estimates are included in the analysis, however, validity necessarily suffers. An accepted procedure for dealing with uncertainty is to conduct a sensitivity analysis, a study of the impact of changes in assumptions on the findings of the evaluation. If the results of the analysis are insensitive across the entire reasonable range of correct values (that is, the most preferred alternative remains so regardless of assumptions), then its findings can be considered valid.

Using the framework

The five components of economic evaluation described above define the analysis. In structuring an evaluation, it is necessary precisely and fully to define the alternative strategies, specify the population to which the alternative strategies will apply, determine the consequences to be included and the methods of measurement, select methods of aggregating consequences over time and across individuals, and identify those estimates whose validity is sufficiently suspect to warrant sensitivity analysis. These steps will be applied in the next sections as the use of economic evaluation for analysis of genetic screening and cytogenetic monitoring is explored.

Economic evaluation of genetic screening

To carry out an economic evaluation of genetic screening in the workplace, the following kinds of information must be available:

- a detailed description of the proposed testing strategy, including followup procedures,
- estimates of the prevalence of the genetic trait in the worker population under study, and
- estimates of the differential effect of worksite exposure on the incidence and severity of disease in the target population.

Genetic screening programs consist of a family of strategies for identifying and reducing exposure of workers with particular genetic traits. A strategy may or may not include counseling of workers with positive test results. The costs and benefits of any such program will depend not only on the type of screening test but also on the followup actions associated with positive and negative test results. For example, a preemployment screening test might result in job denial, whereas a program for employed workers could result in transfer or termination. Alternatively, the choice might be left to the employee, who could remain in the position, request a transfer, or resign. Each of these strategies has different implications for costs and benefits and for the distribution of these consequences among the sectors of society.

The definition of the strategy also depends on the configuration of the screening program itself. Since the tests for detecting genetic conditions are rarely perfectly sensitive or specific but involve some false positive and false negative results, the testing strategy may well include retesting of all those with initial positive results. Or, when two or more different tests, one more costly than another, are available to detect a condition, the testing strategy might consist of a broad screening with the less costly procedure and using the more expensive test to retest positives. Program costs will depend on the configuration selected.

The prevalence of genetic traits in worker populations also may vary. Some susceptible workers may self-select themselves out of high-risk environments. Therefore, reliable data on the prevalence of a trait in given populations is not always available.

The benefits of a genetic screening strategy presumably are manifested in the reduced incidence of the disease associated with the genetic trait.

A necessary condition for such an impact is that the person with the condition be truly at enhanced risk because of exposure to hazardous substances found in the work environment, and the followup action must reduce the probability of the disease. Thus, the complicated chain of relationships between the existence of a genetic trait, occupational exposure to a hazardous agent, and disease onset must be known if the effects of a strategy on worker health are to be estimated. At present, the evidence is generally inadequate to assess the relationship between genetic traits and increased susceptibility to industrial exposure. Yet, even lacking data on these basic relationships, economic evaluation can provide some insights that may assist in decisionmaking regarding the use of genetic screening.

As an example of how economic evaluation might proceed, consider screening for heterozygous serum alpha$_1$-antitrypsin (SAT) deficiency in work environments containing respiratory irritants. This condition has been selected as an example because estimates of its prevalence in the general population are available and some work has been done to estimate the economic costs of the illness it may provoke—emphysema. Evidence has accumulated that people who display an intermediate deficiency of SAT are at increased risk of developing emphysema. Assume for the purposes of this example that a correlation has been shown between intermediate SAT deficiency and an increased risk for respiratory disease in work environments containing respiratory irritants. About 3 to 4 percent of the population in the United States is thought to have this genetic condition. Tests for SAT deficiency are relatively inexpensive. Suppose a large-scale screening program could be implemented for $20 per person. The cost of screening 1,000 workers, then, would be $20,000. Assume also that a worker with a positive test result is removed from an environment containing respiratory irritants. The following question can be asked: How many cases of emphysema would have to be prevented or delayed by such an action to make the test program pay for itself in direct and indirect benefits? The direct and indirect costs of emphysema in 1979 were estimated at $1,300 per person* (10). If this estimate is accepted as accurate, the screening program would have to prevent 15.3 cases of emphysema (in the 1,000 workers screened) in order to pay for itself in direct and indirect cost savings. This implies that emphysema would have to be prevented in 37 to 50 percent of the SAT-deficient workers detected in the screening program.

Since estimates of the average cost of a SAT screening test and the direct and indirect costs of emphysema are uncertain, an analysis of the sensitivity of the break-even point to different values of these parameters is shown in table 17. The practical lower limit of the average cost of a genetic screening test is about $5.** At this unit cost, the break-even number of cases declines to 8 to 16 percent of the SAT-deficient population. Although there are no epidemiological studies relating different levels of exposure to respiratory irritants in work environments with increased risks of emphysema in SAT-deficient individuals,

Table 17.—Hypothetical Break-Even Number of Cases Averted by SAT Testing per 1,000 Workers (break-even percent of SAT-deficient workers)

Direct and indirect cost of emphysema	Cost per test	
	$20	$5
$1,040	19.2 (49-64%)	4.8 (12-16%)
$1,300	15.3 (37-50%)	3.8 (10-13%)
$1,560	12.8 (32-43%)	3.2 (8-10%)

SOURCE: Office of Technology Assessment.

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*This estimate is only a rough approximation of the discounted lifetime costs associated with a new case of emphysema. It is an estimate of the costs incurred in 1979 by all then-extant cases of emphysema. These "prevalence costs" overestimate the lifetime costs of a new case because they are not discounted. Conversely, to the extent that the incidence of emphysema has been growing, the total costs in 1979 disproportionately represent the early and presumably less costly stages of the illness. The extent to which these sources of overestimation and underestimation compensate for one another is unknown. Good data on the incidence of emphysema in the United States do not exist; hospitalization rates have been decreasing since 1970, but the prevalence of the condition has been on the increase (9).

**The average unit cost of a worksite hypertension screening program was recently estimated at $6 (13). Since hypertension screening involves minimal equipment and technician time, it is likely that it represents a lower bound on other types of worksite screening tests as well.

it is known that only 10 percent of all SAT heterozygotes will develop the disease (8) and that emphysema may be brought on by multiple causes (5,8). Thus, the likelihood is low that a SAT deficiency screening program can be justified in terms of its impact on direct and indirect benefits. Moreover, additional research into the relationship between exposure and disease is unlikely to change this conclusion, given what is already known about the potential impact of screening on the incidence of emphysema.

This conclusion does not suggest, however, that the SAT screening issue should be put to rest. Psychosocial consequences have not been included in the analysis; these can be extremely important in a debilitating disease like emphysema. Suppose, for example, that a program of screening and subsequent removal of susceptible individuals from exposure is able to prevent emphysema in only 5 percent of SAT-deficient workers who would otherwise be exposed. This implies that society would incur a net direct and indirect cost of $1,460 to $11,800 for each case of emphysema prevented, depending on assumptions about screening costs, direct and indirect illness costs, and the frequency of SAT-deficient heterozygotes in the population tested. Is it worth up to $10,000 to prevent the psychosocial consequences of a case of emphysema? And how do these psychosocial costs compare to the psychosocial costs of a positive finding on a genetic screening test? Positive test results, whether correct or incorrect, may cause anxiety and disruption to people's lives (that is, psychosocial costs). This is especially true if workers are denied jobs or lose self-esteem because they are labeled as "susceptible." Thus, the $1,460 to $11,800 net direct and indirect cost per case averted cannot be measured against only one type of psychosocial cost.

Note also that the different categories of cost would be borne by different actors. The costs of screening might be incurred by the employer (and ultimately in part by the public in higher prices) or by the government. The direct and indirect benefits would be shared by the individual worker and the public (through impacts on health insurance and disability programs). The psychosocial costs and benefits primarily accrue to workers themselves. Thus, the immediate monetary costs of a screening program are borne by the employer and the public, while the worker and the general public stand to gain monetary benefits in the future and workers may gain psychosocial benefits in the future at the expense of monetary and psychosocial costs in the near term.

It is interesting to compare the principles of economic evaluation with a set of criteria suggested by Stokinger and Scheel for applying genetic screening to the workplace (14). These investigators listed the following conditions that should be met for a genetic screening to be appropriate:

- the condition detected by the test should have a relatively high prevalence in the worker population;
- people with the condition should be susceptible to agents commonly occurring in industry;
- the genetic condition should be compatible with an apparently normal life until exposure occurs; and
- the test should be simple, inexpensive, and amenable to large-scale use.

These conditions are consistent with but more rigid than economic analysis. For example, it might be highly cost effective to screen for a rare condition if the testing cost is low and the health effects of exposure reduction are very large. The conditions of Stokinger and Scheel do not make such tradeoffs explicit, whereas an economic evaluation does.

The prevalence of a trait can be so high that genetic screening becomes impractical. A program consisting of genetic screening with subsequent removal of the worker from the high exposure environment must then be compared with other strategies for reducing exposure levels of all workers. If, for example, 70 percent of all workers are susceptible, it may be more cost effective to take general action to reduce exposure of all workers. How high the prevalence must become before screening is eclipsed by more general exposure reduction strategies depends on the particular situation. For example, slow acetylation rates have been linked to aromatic amine-induced cancer. Approximately 12,000 workers were exposed to these chemicals in the workplace in 1974

(15). Yet, about 50 percent of the U.S. population have slow rates of acetylation. Thus, it may be more effective to reduce exposure levels to all workers than to remove about half of the workers from the potential labor pool. The feasibility of either alternative would depend on the pervasiveness of exposure to the offending chemicals and the technical barriers to reducing ambient exposure levels. Of course, much more information would be needed before such an hypothesis could be accepted or rejected, but the question could be addressed through economic evaluation of the relevant alternatives.

Whether one sees the SAT example given above as informative or misleading depends on expectations about the use to which the information will be put in decisionmaking. Critics of cost-benefit and cost-effectiveness analyses claim that incomplete analyses such as that provided above are given too much attention merely because the results are in a quantified form. Moreover, the unquantified effects, despite their importance, tend to be ignored because they are bothersome. Supporters of the approach would claim that the analysis clarifies the central tradeoff between net direct and indirect costs to society and psychosocial benefits and costs to workers. Both sides would agree, however, that economic evaluation is severely, perhaps fatally, flawed when substantial uncertainty is present in the central estimates of effectiveness or benefit. Sensitivity analysis can remove some of the limitations, but when the results of the analysis are highly sensitive to estimates of cost or effectiveness, as they are in the case of SAT testing, economic analysis is of limited usefulness.

Economic evaluation of cytogenetic monitoring

The case for using cytogenetic studies to monitor workplace exposure to hazardous material rests on the hypothesis that exposure to mutagenic or carcinogenic agents is related to somatic chromosomal damage, which is in turn correlated with an increased risk of disease. If this hypothesis is accepted and particularly if the relationship between exposure level, degree of chromosomal damage, and risk of disease is known and quantified, then cytogenetic tests might be used as biological monitoring devices for workplace hazards.

The potential uses of cytogenetic monitoring are to identify carcinogenic agents and to identify populations at risk due to overexposure to these agents. Ultimately it might be possible to use the tests to develop standards for safe levels of occupational exposure to chemicals and radiation.

It is difficult to lay out a specific strategy for evaluation of a cytogenetic monitoring program because of the profound lack of knowledge about the relationships between occupational exposure, chromosomal damage, and disease in human populations. For the sake of discussion, however, let us suppose that the research evidence were sufficient at this time to justify the use of cytogenetic monitoring to identify carcinogenic agents. Suppose that it has been established that there is a high correlation between chromosomal damage in a group and subsequent cancer rates. Then, employers might establish programs for periodic monitoring of workers who are routinely exposed to industrial chemicals. The cost of such a program would be highly sensitive to features such as the frequency of testing (that is, monthly, quarterly, yearly), the sample size in each testing period, the methods of recordkeeping and quality control, and the actual cytogenetic procedures employed. Cytogenetic studies are relatively expensive laboratory procedures. The estimated cost is between $100 and $300 per test, depending on a laboratory's volume and organization, although testing costs may be reduced in the future with the development of automated methods. At an average cost per test of $100, however, the features of the monitoring program make an enormous difference in program costs. For example, testing 500 workers once each year would cost $50,000, whereas a quarterly testing program of the same number of workers would cost $200,000 annually.

Both the costs and benefits of a monitoring program depend on the actions taken on the basis of its results. If significant chromosomal damage were followed by removal of the chemical from the workplace or some other method of exposure reduction, the major hypothesized benefit would be a reduction in the rate of exposure-induced cancer. The costs of exposure reduction would depend on the technical and economic relationships in the production process. If no action were taken, neither benefits nor additional costs would ensue. It is reasonable to assume that an expensive monitoring program would be undertaken only if some benefits could be expected; therefore, a program for exposure reduction must be assumed to be a natural sequel to cytogenetic monitoring.

To estimate the economic benefits of cytogenetic monitoring programs, it is necessary to know, or at least to estimate, the probability that the agents found in the monitored workplaces will be found to produce chromosomal damage. Further, precise analysis would demand that the impact of exposure on cancer rates be estimated with reasonable certainty. But if the latter were known, the need for a monitoring program of the type outlined above is questionable. Thus, the prospects are poor for reasonably accurate a priori estimates of the health effects, and hence benefits, of cytogenetic monitoring.

Though it is not possible now, and may never be, to estimate the benefits of cytogenetic monitoring with any precision, it is useful to consider the order of magnitude of the economic benefits that would result from each case of cancer that might be prevented by such a program. The direct and indirect costs per case of cancer were estimated in 1978 at about $22,000, consisting of $5,000 in direct and $17,000 in indirect costs* (12). These costs vary with the age of onset and the type of cancer, but they can be taken as a general guide to the order of magnitude of the monetary benefits associated with each case of cancer prevented. In a pioneering but highly speculative study, Abt attempted to estimate the combined indirect and psychosocial costs of cancer (1). These costs were estimated at $137,000 per case. Thus, even though this estimate is based largely on assumptions and rules of thumb, it illustrates the overwhelming importance of psychosocial costs in the consequences of cancer.

The stakes are clearly high on both sides of the issue. The costs of cytogenetic monitoring are potentially high, but the costs of cancer are also high. At present there is insufficient evidence to assess the value of cytogenetic monitoring because the relationships between chromosomal damage and clinically relevant effects have not been demonstrated. Yet, the magnitude of the costs involved argues for increased research into these relationships.

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*These are prevalence costs. Possible sources of inaccuracy in these estimates are discussed in an earlier footnote.

Conclusion

Cost-benefit and cost-effectiveness analyses are economic methodologies that can be useful in structuring the analysis involved in decisionmaking and in assessing the desirability of alternative outcomes. The significant uncertainties associated with genetic testing, particularly the limited evidence of an association between endpoints and risk of disease, preclude the rigorous application of these tools to this technology. However, these tools can help identify the uncertainties involved and provide a rough sense of the benefits, burdens, and tradeoffs associated with genetic testing programs.

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Part V

Congressional Issues and Options

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Chapter 11

Issues and Options

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Chapter 11

Issues and Options

Genetic testing is an emerging technology. It has the long range potential to play a role in the prevention of occupational disease, but it also has the potential for misuse. Although only a handful of companies are using genetic testing now, many more are interested. Current law provides some incentive for its use and some safeguards against its misuse. Established ethical principles also provide some guidance for its use. However, many questions remain unanswered. Under these circumstances, it may be appropriate for Congress to balance the competing interests and to make the value judgments necessary in order to maximize the technology's potential benefits and minimize its risks.

This chapter provides an array of issues and options for congressional consideration. They may be grouped loosely around the following fundamental policy questions:

- Should the technology be stimulated and, if so, how?
- Should there by any constraints on the use of the tests and, if so, what?
- To what degree should society protect workers who are at increased risk for developing disease, at what cost, and who should bear that cost?

The first issue is an overview of the options related to all of these questions. The issues and options that follow focus on particular aspects.

ISSUE: What actions could Congress take with respect to genetic testing in the workplace?

OPTIONS:

A. Maintain the status quo.

Congress could choose not to take any action to stimulate, constrain, or regulate genetic testing. This would allow private parties to continue research into the merits of the technology. Constraints on its use would develop through court rulings in lawsuits between these parties or by negotiations between companies and unions. Interested congressional committees could continue their practice of holding oversight hearings to raise the issues for public discussion.

The primary argument supporting this option would be the view that congressional action would be premature. The technology is not being widely used, and it is primarily in the research phase of its development. In addition, there are existing constraints on its potential misuse. These include the possibility of lawsuits and adverse publicity. Finally, much of the important information necessary for legislation is unavailable because it is unknown. For genetic screening techniques, this information includes the number of workers who might be genetically predisposed to disease, the extent to which they might face adverse employment actions, the availability of other employment opportunities, and the cost of safeguarding these workers. For genetic monitoring techniques, this information includes their predictive value, the extent to which they might be used, and the costs associated with either using or not using them.

The arguments against this option relate to how society controls an emerging technology. Many policy decisions will need to be made with respect to genetic testing, and arguably Congress is a better forum for doing so than the courts or private parties. Congress can gather all information and viewpoints and then balance the conflicting interests. In addition, while the courts often play a major regulatory role for any technology, they are limited in their ability to encourage the development of a technology in a positive manner. However, Congress can do so by providing funds for research or other incentives.

B. Stimulate the technology's development and use.

Congress could stimulate the technology by providing additional money for research on the techniques, for epidemiological studies to determine associations between genetic indicators and disease, and for basic research on the cause of occupational disease in general. If genetic testing could be developed to the point where the tests are predictive of an individual's or group's increased risk for occupational illness, its use could result in a number of direct and indirect benefits. The principal direct benefit would be a lower incidence of occupational disease among workers. They and their families would be spared some of the pain, cost, and emotional trauma that accompany illness. In addition, employers would save some of their direct and indirect costs of occupational disease—employee time lost from work, insurance premiums, legal fees, and monetary damages assessed in lawsuits. Society would benefit through the greater health and productivity of its work force. A major indirect benefit of developing this technology might be a greater understanding of the causes of occupational disease and disease in general.

The principal argument against this option is the concern about the potential misuse of the technology and about potential adverse impacts. Some of these concerns relate to unfair employment discrimination and attention being directed away from other ways to address occupational diseases. These concerns might be dispelled by regulation to direct the technology's development in socially desirable ways. In fact, if the tests were highly predictive of future illness, the Occupational Safety and Health Administration (OSHA) could require their use and constrain how they were used, so long as those constraints were shown to enhance worker health and were not directed toward prohibiting fair employment practices.

Another drawback to this option is the fact that there is no information on the amount of occupational disease that could be prevented by genetic testing, even if the tests were reliable predictors of disease. Similarly, there is no information on what it would cost to get the tests to the point of clinical usefulness.

C. Prohibit the use of genetic testing in the workplace.

The principal reason for prohibiting genetic testing in the workplace would be concern over its potential misuse, particularly at its current stage of development where its ability to predict future disease has not been demonstrated. This potential for misuse probably would be greater for genetic screening than for genetic monitoring because the former is targeted toward identifying individuals at increased risk while the latter focuses on groups at increased risk. However, concern exists that employers might use either screening or monitoring to exclude individuals from jobs. Existing law may offer protection in some circumstances, but there are many questions to be resolved. The collective bargaining process could be used by unions to negotiate protection for workers, but the primary focus of bargaining has been economic matters. While health matters have also been important, genetic engineering apparently has not been a bargaining issue. In addition, most of the work force is not unionized. Moreover, these remedies are not helpful if a susceptible person does not know why he or she was denied a job. Finally, while ethical principles provide guidance for the proper use of this technology, it is difficult to know if they are being followed.

The principal drawback to this option is that it is a drastic solution to the problem of potential misuse. Genetic testing does not appear to be widely used. Law, ethics, and public opinion provide incentives against its misuse. Moreover, banning its use would prevent research that might determine its usefulness in preventing occupational disease or provide basic knowledge about occupational disease.

Another argument in favor of this option would be the claim that an employee's risk of future illness is not an appropriate factor for job selection, even if screening or monitoring were highly predictive. Employees have no control over their genetic makeup and generally have no control over previous exposures to harmful agents. In addition, their increased risk would not affect their current ability to do the job.

There are at least two counterarguments to the assertion that risk of illness should not be a job selection factor. First, society accepts the proposition that immutable characteristics can be proper criteria for employment selection. Intelligence is at least an implicit selection criterion for many professional jobs and physical attributes are exceedingly important for jobs ranging from professional basketball to neurosurgery. Second, this viewpoint places the autonomy interests of the individual above the interests of society in lowering the costs of occupational illness even when it may not be feasible to take other steps, such as lowering exposure.

D. Regulate the technology.

This option represents a judgment that any risks presented by the technology can be controlled and that the claimed benefits will be of value to society. The option would permit research to continue, yet constrain the manner in which genetic testing is used. One type of constraint would be limitations on what job actions employers could take on the basis of test results. Another type of constraint would be a requirement that the tests meet minimum standards of scientific validity before employment decisions were made on the basis of the results. Such a statute need not specify detailed standards; it could adopt a standard such as "reasonably predictive of future illness" and allow the appropriate agency to provide details.

This option has the advantage of addressing the potential risks of genetic testing immediately and in a comprehensive manner rather than waiting for the law to develop on a case-by-case basis through the courts. Congress may be uniquely able to study the problem fully, balance competing interests, and provide comprehensive yet targeted solutions.

A possible drawback of this option is that the problem may not yet be "ripe" for congressional action. On the basis of available evidence, genetic testing in the workplace does not appear to be widespread. Moreover, there is no available evidence about: 1) the number of workers who potentially could be screened or monitored if the tests were sufficiently predictive, 2) the number who might be excluded from jobs, 3) the ease with which excluded workers could find comparable jobs, and 4) the costs of various regulatory alternatives. On the other hand, congressional action now could prevent potential misuse before the technology becomes widespread, and legislation could create a mechanism for gathering some of the presently unavailable data.

E. Encourage the development of voluntary guidelines on the acceptable use of genetic testing.

Congress could ask the National Academy of Sciences or a similar body to establish a special commission of representatives from industry, labor, academia, and other sectors of society to draft guidelines for the use of the tests. This would allow the parties most involved to make the difficult value judgments in balancing competing interests and would avoid direct governmental regulation.

ISSUE: How could Congress regulate genetic testing in the workplace?

OPTIONS:

A. Constrain employment actions that may be taken on the basis of genetic testing.

Congress could address many of the concerns raised by genetic testing by regulating how emloyers may use the results of the tests, even if they were highly predictive. The following represents some possible elements of such an approach: 1) prohibit job exclusion on the basis of genetic makeup or genetic damage, 2) prohibit job transfers because of genetic makeup or genetic damage unless the transfer were to a comparable job at comparable pay and benefits, 3) require strict confidentiality of medical information, and 4) require that employees be told the results of testing and be given counseling.

This option would clearly protect the interests of workers, preventing potentially serious consequences to individuals who have no control over the reason for discrimination against them. In addition, no difficult judgment would have to be made as to how predictive the tests should be before they are permitted.

There are at least two major disadvantages to this option. First, it may be too broad. If not carefully drafted, a statute could reach genetic diseases (not traits) that do affect an employee's current ability to perform the job safely and effectively. It is generally accepted that inability to perform a job, even for medical reasons, is a valid criterion for job selection. Second, if workers with certain traits were in fact predisposed to occupational illnesses and chose to ignore that information, the additional direct and indirect costs of their illnesses eventually would be borne by society. This would be the case even if employers were required to install additional engineering controls, since the costs of those controls would be passed on to society. On the other hand, if excluded workers were unable to find comparable jobs, society would bear the costs of lost productivity and possibly additional unemployment payments. The answer to the question of who should bear the costs associated with genetically predisposed or damaged individuals will depend not only on economic analyses but on prevailing political views of distributive justice.

B. *Prohibit employment decisions on the basis of genetic testing unless the employer can demonstrate that the results are reasonably (or substantially) predictive of future illnesses.*

This option places the burden on an employer to justify the claimed correlation between test results and risk of illness. The specific criteria for meeting a necessarily general statutory standard could be provided by agency regulation and case law.

There are several advantages to this option, especially when compared to option A. First, it focuses on the immediate concern of job denial on the basis of poorly predictive tests, thus protecting employees' interests. Second, it protects employers' interests in lowering their costs from occupational diseases, by excluding workers when there is a rational, scientific basis for doing so. Third, it would allow research on the techniques to continue.

The principal drawback of this option is that it could be a de facto determination without a full public debate that future risk of illness is a proper job selection criterion. On the other hand, there is a substantial lack of the type of information desirable for deciding this fundamental issue at this time.

C. *Amend the Rehabilitation Act of 1973 to state that genetic makeup is a handicap and clarify whether individuals who are genetically predisposed to illness are considered to be "otherwise qualified" within the meaning of that act.*

A major advantage of this option would be working with an existing statute rather than devising an entirely new one. Sections 503 and 504 of the Rehabilitation Act deal with problems that conceptually are very similar to those posed by genetic screening. If applied to genetic screening, the act would require at a minimum that the tests be reasonably predictive of future illness.

On the other hand, this option would force legislative activity into an existing statutory framework that may not be completely suited to genetic screening. The Rehabilitation Act was designed to bring millions of handicapped people into the mainstream of American life. Genetic screening has not created a problem anywhere close to the magnitude of that addressed by the Rehabilitation Act. Moreover, section 503 requires employers to take affirmative action to employ the handicapped. Congress may not wish to require affirmative action to employ people who are genetically predisposed to occupational illness, if that predisposition can, in fact, be demonstrated.

D. *Require that research on employees be done according to existing Federal regulations designed to protect human subjects of research.*

The Department of Health and Human Services has promulgated regulations governing federally funded biomedical and behavioral research on humans. The regulations contain provisions designed to protect the interests of the research subjects. Requiring private companies to follow these regulations in research involving genetic testing or any other kind of research done in the workplace would mitigate the potential for abuse.

E. *Require full disclosure to employees and their representatives of the nature and purpose of all medical procedures performed on employees.*

Under current law, employees and unions have access to employee medical records, but employers are not required to disclose the nature and purpose of medical procedures and how the results are used. Required disclosure of this information to the employee at the time the procedure was being performed would be a strong incentive to employers for self-regulation. If workers and their medical advisors had full knowledge of a company's medical procedures, they could take steps to prevent abuses, through negotiation or legal action. Publicity alone could prevent the worst abuses. This would also protect the autonomy interests of workers by allowing them to be part of a decisionmaking process that affects their health and economic interests. Some of the arguments against this option would be that it might be burdensome and costly for employers and that it would intrude too much on the professional judgment of the occupational medical specialist.

ISSUE: How could Congress foster the development and use of this technology?

OPTIONS:

A. Fund research for the development of tests with high reliability and validity.

Genetic variability and differential susceptibility to toxic chemicals are well-established concepts in the scientific literature. Currently, there are many genetic screening tests that could be done in a workplace setting to detect potentially susceptible individuals. For the most part, these tests are reliable and valid for identifying the genetic traits in question; a notable exception is the test for aryl hydrocarbon hydroxylase (AHH) inducibility. Research on developing tests for those traits that are more prevalent in the population should receive higher priority because they are more likely to have a high predictive value. The only test covered in this report that falls into this category is AHH inducibility.

With respect to genetic monitoring, it is less well established scientifically that exposure to toxic chemicals and ionizing radiation can cause genetic damage in humans, although there is an overwhelming amount of evidence that this is true in experimental mammals. Not known at all is the impact of genetic damage on one's risk for disease, especially cancer, or on future generations, yet the current thinking of the scientific community is that increased amounts of genetic damage is generally deleterious.

Alternatives are needed to the time-consuming cytogenetic tests currently in use. If genetic monitoring is to be done on a large scale, the availability of automated tests becomes important. The development of various noncytogenetic methods could be useful in this respect. Those that show promise currently include tests for detection of: mutagens in urine, alkylated hemoglobin, HGPRT mutation in lymphocytes, hemoglobin mutations, chemically damaged deoxyribonucleic acid bases, and LDH-X variants in sperm. For both cytogenetic and noncytogenetic tests, a better understanding of the factors that contribute to genetic damage in the absence of occupational exposure is needed (that is, a "normal" or baseline response) in order for the tests on exposed populations to be meaningful.

The government agencies which could be involved in these studies include the Environmental Protection Agency (EPA), the National Institute for Occupational Safety and Health (NIOSH), and the National Institute for Environmental Health and Safety (NIEHS).

B. Fund epidemiologic studies in occupational settings directed by NIOSH or NIEHS.

Data are most lacking concerning the correlation of genetic traits or genetic damage to an increased risk for disease. Epidemiologic studies in an occupational setting can address this problem. If these studies were to be undertaken, they must use good epidemiological practices and document exposures. Studies should only be undertaken if they are likely to yield statistically reliable data. For instance, genetic monitoring studies would require exposure levels high enough to yield a clear-cut statistical response between exposed and nonexposed groups without having to use excessively large numbers of people. Especially important would be to establish a dose-response relationship. Genetic screening studies would have to focus on genetic traits that have a significant prevalence in the population (greater than 1 percent).

Epidemiologic studies are very costly and difficult to control, especially if they run over long time periods. Some genetic screening studies could be done in a short time (1 to 3 years) once a population with the trait was selected because, presumably, the symptoms of disease resulting from exposure would manifest themselves soon after exposure. These traits include the red blood cell traits. Most of the other traits reviewed here are potentially correlated with diseases which have a long latent period, such as emphysema and cancer. To assess correctly the exposure information with the disease endpoint, much longer epidemiologic studies (10 to 30 years) are necessary.

For genetic screening, higher priority should be given to studies on traits with a high prevalence in the population. These include SAT deficiency, AHH inducibility, carbon oxidation ability, and the association of particular human leukocyte antigens with risk for disease.

Epidemiologic studies using genetic monitoring techniques would have to be long term in order to determine the association between genetic damage and cancer. The chemicals chosen for study would have to be selected carefully. Many of the agents discussed in this report are known already to cause cancer in humans (for example, ionizing radiation, benzene, vinyl chloride), and occupational exposure to these is very low and possibly not detectable by the genetic techniques now in use.

C. Establish a federally funded data bank, directed by NIOHS, EPA, or NIEHS, to be used in the study of the causes of differential susceptibility to occupational disease.

Because the study of the effects of harmful agents includes many scientific disciplines, it would be useful to have the relevant data collected in an accessible location. This computerized data bank could include not only genetic factors affecting toxicity, but developmental, aging, nutritional, and lifestyle factors as well. The data bank would include epidemiologic studies that have been or are being done in occupational settings, either governmentally or privately funded (somewhat in the same manner as EPA's Gene-Tox Program). Those working in the field of genetic toxicology could draw on the information in the bank in order to design studies and to prevent duplication of effort. The toxicology data would be of considerable value to various regulatory agencies in their standard setting.

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Appendix A

Survey Design and Methodology

Study design

SOURCE OF DATA

The survey was conducted for OTA from February 25 to June 8, 1982, by the National Opinion Research Center (NORC), a nonprofit survey research corporation affiliated with the University of Chicago. NORC sent confidential questionnaires to the chief executive officers of the 500 largest U.S. industrial companies,[*] the chief executive officers of the 50 largest private utility companies,[**] and the presidents of the 11 major unions that represent the largest numbers of employees in those companies.[***]

These recipients were selected based on discussions with industry scientists who indicated that a company's size rather than its major product line would more likely be the determining factor for testing. Moreover, hazardous substances are found throughout the industrial sector, including utilities, not just in the chemical industry. A company's decision to implement genetic testing most likely would be based on the extent and sophistication of its medical program, and sophisticated programs most probably would be found in large companies. Further, because unions also are interested in the health of their members, they were thought to be a potential source for undertaking such programs. All 561 recipients were surveyed, rather than just a sample, in order to eliminate sampling error that might result from a small number of companies testing and to avoid other potential problems associated with sample selection

QUESTIONNAIRE

Development.—A questionnaire addressing the purposes of the study was developed by the OTA staff and NORC over a period of approximately 2 months, during which it was extensively reviewed and revised. Reviewers for technical accuracy included individuals in science, medicine, and law, and persons affiliated with the American Industrial Health Council, the Chemical Manufacturers Association, the American Occupational Medical Association, the American Academy of Occupational Medicine, and the Genetic Toxicology Association.[****] Their comments were evaluated for objectivity and relevance to the purpose of the survey. The questionnaire then was revised to reflect the results of the review and prepared for pretest.

The bottom 25 companies in the Fortune 500 were selected for the pretesting phase, which was administered from February 25 to March 12, 1982. Eleven (44 percent) of the 25 companies responded. Analysis of the results indicated that the questionnaire was reasonably clear and consistent and that it should provide the data sought. A draft of the final instrument was reviewed by the OTA project panel, which included representatives from industry, academia, and labor. Minor format changes were made, and two questions were deleted. The rest of the survey population was questioned from March 23 to June 8, 1982. Because the questionnaire's changes were relatively minor, the pretest responses were included in the final analysis.

Instrument.—The questionnaire is a four-page printed instrument. Two slightly different versions were used, depending on whether the document was sent to a company or a union; however, the differences are semantic in nature. (See app. C.) The questionnaire was composed of:

- introductory paragraphs, which give instructions and define terminology;
- eight questions on genetic screening and eight on cytogenetic monitoring;[*]
- a question on actions taken as a result of either type of testing;
- a question relating to the use or development of genetic tests in animal studies;
- a question to determine the major industrial sector in which the companies did business; and
- a space for explaining the answer to any question or providing additional information.

The questionnaire reflected two assumptions. One was that the individual who would respond to the questionnaire would be familiar with genetic testing. This assumption was believed to be appropriate because genetic testing has been widely discussed by various professional groups concerned with occupational health, including committees within major industrial trade associations. The second was that the definitions of genetic screening and cytogenetic monitoring would be carefully and consistently followed in answering the questionnaire. Because different experts use the terminology in slightly different ways, these terms were defined in the first paragraph of the questionnaire. No reason or evidence was found to invalidate these assumptions.

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[*] Identified by Fortune 500 listing of U.S. companies engaged in manufacturing/mining; Fortune, vol. 103, No. 9, May 4, 1981.

[**] Identified by Fortune Magazine List C; Fortune Magazine, vol. 103, No. 9, May 4, 1981.

[***] Identified in the Directory of National Unions and Employees Association (1979) by the U.S Department of Labor.

[****] In view of time constraints, these people gave their opinions as individuals rather than as representatives of their organization.

[*] The questionnaire used slightly different terminology for the tests than used in this report. It used the term "biochemical genetic testing" to refer to genetic screening and the term "cytogenetic testing" to refer to cytogenetic monitoring.

Confidentiality.—Providing confidentiality to the individuals answering the survey was viewed as crucial for securing both a high rate of participation and accurate information, particularly in view of the sensitive nature of the subject (1). No identifying marks were placed on the questionnaire, and respondents were urged not to do so on their own. Results could be compiled only in aggregate form. Followup procedures were possible because respondents were asked to return, separate from the questionnaire, post cards that named their organization and stated that the questionnaire had been completed and returned.

SURVEY

The questionnaires were sent to 561 chief executive officers and presidents, with the suggestion that they route it to the person responsible for health and safety matters. This approach sought to demonstrate the importance of the survey and to ensure that the questionnaire quickly got to the appropriate person in the organization, thereby increasing the chances of a timely response.

Questionnaires were accompanied by two one-page letters—one from OTA's Director, John H. Gibbons, and one from NORC's project director, Cynthia Thomas—and by a post card and a return envelope. A list of the names of the members of the project's advisory panel also was enclosed. (See app. C for copies of the questionnaire, letters, and advisory panel membership list.)

NORC began followup procedures on April 19 by sending 98 letters to nonrespondents. A second effort involved telephone calls to 200 of the nonrespondents. The effort concentrated on the top 100 companies of the Fortune listing and on those in key industrial groups, such as chemicals, rubber and plastic products, metal manufacturing, and pharmaceuticals.

By the June 8, 1982, cutoff date, 366 organizations had answered the questionnaire, a 65.2-percent response rate, and 26 organizations had specifically declined to do so, a 4.6-percent refusal rate. Those who declined generally gave either no reason for refusal or the reason of corporate policy not to respond to surveys. Questionnaires from seven more organizations were received after the cutoff date. None of these organizations reported any testing activity and were not substantially different from the earlier respondents. Since these reponses were received after the close of the survey period, they are included as nonrespondents for analysis purposes.

Response pattern

Can the results of this survey be generalized to the population of Fortune 500 companies, large utility companies, and major unions? An answer to this involves two additional questions: Are the responses equally distributed among the groups represented in the survey? Are characteristics of the respondents different from the nonrespondents? These two questions are discussed in turn.

Two weeks into the survey, April 13, 1982, approximately one-third (30.5 percent) of the contacted organizations returned the post card indicating they had participated in the survey. At that time, little variation was seen in the response rate by size or type of organization. The largest discrepancy was between the unions, with a 27.3-percent response rate, and the utility companies, with a 38-percent response rate. By the close of the survey (June 8, 1982), however, the discrepancy in response rate became quite noticeable. The large corporations had the highest response rates: 68 percent for utilities and 61.5 percent for the top 200 companies in the Fortune 500 listing; the unions and small corporations had the lowest response rates: 36.4 percent for unions and 44 percent among the bottom 300 companies in the Fortune 500 listing. (See table A-1.) The variation in response pattern between

Table A-1.—Distribution of Returned Post Cards by Organization Size and Type

	Cumulative number of post cards received by:					
	Apr. 13, 1982			June 8, 1982		
Organization size/type	Yes	No	Percent received	Yes	No	Percent received
Fortune 500 companies						
Top 200	65	135	32.5%	123	77	61.5%
Bottom 300	84	216	28.0	132	168	44.0
Utilities: top 50	19	31	38.0	34	16	68.0
Unions: 11	3	8	27.3	4	7	36.4
Total: 561	171		30.5%	293		52.2%

SOURCE: National Opinion Research Center, survey conducted for OTA, 1982.

April 13 and June 8 is undoubtedly due to a number of factors, most probably the followup efforts which began in the third week of the survey and focused on the top 100 companies of the Fortune 500 listing and organizations in selected industrial classifications such as utilities. Thus, the results of this survey may be more applicable to the larger manufacturing/mining and utility companies than to smaller manufacturing/mining companies and unions.

Analysis of selected characteristics of respondents compared with nonrespondents is limited to the Fortune 500 companies. Nonrespondents were identified by the process of elimination using the post card responses. The 193 nonrespondents included the 38 companies that sent in anonymous questionnaires but no post card. Respondents and nonrespondents were compared on the following characteristics: geographic location, size of organization, and type of industry. Rates of response and nonresponse did not differ greatly geographically. (See table A-2.) The largest variation occurred among the Central States where a 5-percentage-point variation occurred between the nonrespondents and the respondents. For size of company, however, the rate of nonresponses did differ widely from the rate of responses. (See table A-3.) For example, 53 percent of the nonrespondents were in the smallest companies, compared with 32 percent of the respondents. This discrepancy was not unexpected, because the followup concentrated on larger companies and the response rates may reflect these efforts. Rate of nonresponse did not vary greatly from rate of response with respect to industry classification. (See table A-4.) Eleven industries had a slightly higher rate of response than predicted, as evidenced by a comparison with the expected response rate (total company rate). Of these industries, five (chemicals, petroleum refining, rubber and plastic products, metal manufacturing, and pharmaceuticals) were the key industries selected for followup activities and the rates for the remaining six (glass/concrete, electronics, measuring equipment, motor vehicles, aerospace, and office equipment) may be explained by such factors as the effect of followup based on size of company or chance.

Thus, whereas the results of the survey may be more representative of the larger manufacturing/

Table A-2.—Distribution of Nonrespondents, Respondents, and Total Companies by Geographic Location (based on Fortune 500 companies)

	Nonrespondents		Respondents		Total companies	
Geographic location[a]	Number	Percent of total nonrespondents	Number	Percent of total respondents	Number	Percent of total companies
Northeast	82	42%	133	43%	215	43%
Southeast	8	4	22	7	30	6
Central	80	41	111	36	191	38
Mountain	2	1	7	2	9	2
West	21	11	34	11	55	11
Total	193		307		500	

[a] The following are included in the respective geographic locations:
Northeast: Maine, Vermont, New Hampshire, Massachusetts, Connecticut, Rhode Island, New York, New Jersey, Pennsylvania, Maryland, Delaware.
Southeast: Virginia, North Carolina, South Carolina, Georgia, Florida, Alabama, Tennessee, Mississippi, Louisiana,.
Central: North Dakota, South Dakota, Nebraska, Kansas, Oklahoma, Texas, Montana, Iowa, Missouri, Arkansas, Michigan, Wisconsin, Illinois, Indiana, Ohio, Kentucky, West Virginia.
Mountain: Montana, Wyoming, Utah. Colorado, New Mexico, Arizona.
West: Alaska, Hawaii, Washington, Idaho, Oregon, California, Nevada.

SOURCE: National Opinion Research Center, survey conducted for OTA, 1982.

Table A-3.—Distribution of Nonrespondents, Respondents, and Total Companies by Size (based on Fortune 500 companies)

	Nonrespondents		Respondents		Total companies	
Size of company	Number	Percent of total nonrespondents	Number	Percent of total respondents	Number	Percent of total companies
Fortune 100	29	15%	71	23%	100	20%
Fortune 200 and 300	62	32	138	45	200	40
Fortune 400 and 500	102	53	98	32	200	40
Total	193		307		500	

SOURCE: National Opinion Research Center, survey conducted for OTA, 1982.

Table A-4.—Distribution of Nonrespondents, Respondents, and Total Companies by Industry Classification (based on Fortune 500 companies)

Industry classification[a]	Nonrespondents		Respondents		Total companies	
	Number	Percent of total nonrespondents	Number	Percent of total respondents	Number	Percent of total companies
Mining, crude oil	7	3.6%	6	2.0%	13	2.6%
Food	23	11.9	31	10.1	54	10.8
Tobacco	1	0.5	3	1.0	4	0.8
Textile	5	2.6	8	2.6	13	2.6
Apparel	5	2.6	4	1.3	9	1.8
Furniture	1	0.5	0	—	1	0.2
Paper, fiber, wood	16	8.3	14	4.6	30	6.0
Publishing, printing	8	4.1	5	1.6	13	2.6
Chemicals	12	6.2	28	9.1	40	8.0
Petroleum refining	11	5.7	30	9.8	41	8.2
Rubber, plastic	2	1.0	4	1.3	6	1.2
Leather	1	0.5	1	0.3	2	0.4
Glass, concrete	3	1.6	13	4.2	16	3.2
Metal manufacturing	14	7.2	24	7.8	38	7.6
Metal products	11	5.7	12	3.9	23	4.6
Electronics, appliances	12	6.2	25	8.1	37	7.4
Shipbuilding, railroad, and transportation equipment	4	2.1	5	1.6	9	1.8
Measuring equipment	4	2.1	11	3.6	15	3.0
Motor vehicles	6	3.1	13	4.2	19	3.8
Aerospace	3	1.6	11	3.6	14	2.8
Pharmaceuticals	6	3.1	11	3.6	17	3.4
Soaps, cosmetics	3	1.6	5	1.6	8	1.6
Office equipment	3	1.6	10	3.2	13	2.6
Industrial and farm equipment	23	11.9	20	6.5	43	8.6
Musical instruments, toys	3	1.6	2	0.6	5	1.0
Broadcasting, motion pictures	3	1.6	3	1.0	6	1.2
Beverages	3	1.6	8	2.6	11	2.2
Total	193		307		500	

[a] Industrial classification is based on Fortune 500 listing for each company; that listing was the Standard Industrial Classification Code.

SOURCE: National Opinion Research Center, survey conducted for OTA, 1982.

mining corporations and private utility companies as identified in Fortune magazine listings, the respondents do not appear to differ greatly from the nonrespondents in geographic location or type of company.

Appendix A reference

1. Jones, Wesley H , "Generalizing Most Survey Inducement Methods: Population Interactions With Anonymity and Sponsorship," *Public Opinion Quarterly,* spring 1979, p. 108.

Appendix B

Report From the National Opinion Research Center

WORKPLACE SURVEY:

BIOCHEMICAL GENETIC OR CYTOGENETIC
TESTING IN THE WORKPLACE --
PAST, PRESENT AND FUTURE

DRAFT REPORT

Prepared by
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National Opinion Research Center

Submitted to
The Office of Technology Assessment
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SUMMARY

The National Opinion Research Center has conducted a mail survey of the 500 largest U.S. Corporations, 11 unions, and 50 utilities to determine how many organizations have ever engaged in or might be considering the use of biochemical genetic or cytogenetic testing of employees or potential employees. Ultimately, respondents from 373 organizations replied to the questionnaire, either by mail or telephone, yielding a response rate of 64.5%. Twenty-six organizations declined to complete the questionnaire, generally citing reasons of time or survey relevance. Six organizations report that they are presently testing. Two of them are chemical companies, two are utilities and two are in the electronics industry. Seventeen organizations have tested in the past. Only one organization reports current testing but no past testing. Fifty-nine organizations (16.1%) might possibly test in the future.

WORKPLACE SURVEY:

BIOCHEMICAL GENETIC OR CYTOGENETIC TESTING IN THE WORKPLACE -- PAST, PRESENT AND FUTURE

I. INTRODUCTION

The National Opinion Research Center has conducted a mail survey of the 500 largest U.S. corporations, 11 unions, and 50 utilities to determine how many organizations have ever engaged in or might be considering the use of biochemical genetic or cytogenetic testing of employees or potential employees. This survey contributes to a larger research effort conducted by the Office of Technology Assessment for the Committee on Science and Technology of the U.S. House of Representatives. The research questions the survey was designed to address include:

(1) the frequency of past, present and anticipated biochemical and/or cytogenetic testing in the workplace and whether it has been conducted on a routine, special or research basis;

(2) the names of the tests used, for whom, and for what purpose;

(3) the actions, if any, taken by the company on the basis of the results of the tests; and

(4) the criteria against which tests have been measured to determine acceptability for use.

II. METHODOLOGY

During February a pretest draft of the questionnaire was sent by Federal Express to twenty-five organizations in the Fortune 500. The objective was to determine whether the questionnaire could be answered properly and whether a reasonable rate of response could be expected. Without any follow-up, approximately 50% of these organizations returned a completed questionnaire. Since only relatively minor changes in the formatting of the instrument were required, and two items were deleted, we were able to include these responses in the final analysis.

On March 25, 1982, questionnaires were sent to 475 chief executive officers of the largest corporations, presidents of 11 unions and chief executives of 50 utility companies. Questionnaires were accompanied by two one-page letters, one from the Office of Technology Assessment, signed by John Gibbons, the Director, and one from NORC, signed by Cynthia Thomas, NORC's project director, and by a post card and a return envelope. A list of the names of members of an advisory panel to OTA of experts in genetics, occupational medicine, and law, also was enclosed.

The letter from OTA introduced the study by stating that the Committee on Science and Technology of the U.S. House of Representatives had asked for the assistance of leading organizations in completing the questionnaire. The CEOs were asked to direct the questionnaires to their chief executives for health affairs.

NORC's letter mentioned the importance of the study, the confidential nature of the information, and the use of a pre-paid post card to be returned by the respondent indicating that a questionnaire was completed, in order to keep the identity of responding organizations separate from the questionnaires.

Half of the questionnaires were sent by Federal Express and half by first class mail, since the budget for postage was limited. Two hundred cases were targeted for follow-up telephone calls, with priority given to companies in the Fortune 100 and in key industry groups, including those involved in chemicals, rubber and plastic products, metal manufacturing, and pharmaceuticals.

From the pretest, we learned that the office of the chief executive, as suggested in the cover letter, often referred the questionnaire to someone else in the organization, such as a chief medical officer. Sometimes several subsidiaries had to be consulted before the questionnaire could be completed. Consequently, it was realistic to expect the questionnaire to take several weeks or more to be completed after its receipt. To allow enough time for organizations to respond, the first telephone follow-ups during the main field period were scheduled for the week of April 19. Up to and including the 20th of April, 219 post cards and 239 questionnaires had been received.

Telephone follow-up calls were initiated with 200 of the organizations which had not sent in post cards by April 21. The office of the chief executive officer was contacted, the purpose of the study and the urgency of a response was stated, and the respondent, generally an executive secretary or administrative assistant, was asked to determine whether the questionnaire had been received and, if so, who now had it. The procedure usually either resulted in the request for an additional questionnaire, or the identification of one or a series of executives to whom the questionnaire had been referred.

Repeated follow-up calls were made to the offices of those reported to be in possession of the questionnaire, each time allowing a reasonable time period for the respondent to expedite the return of the post card before an additional call was made. Ultimately, 373 questionnaires were returned or the information required to complete them was obtained by telephone or in a letter, yielding a response rate of 64.5%, including the pretest cases. The number of post cards received was 307, including post cards from the pretest. Twenty-six organizations declined to complete the questionnaire (4.6%), generally citing reasons of time or survey relevance.[1] Results presented in the following tables are based on responses received by June 1 (the first 366 cases). No questionnaires received after that date contained any instances of testing. An analysis of non-respondents is presented in Appendix A.

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[1] Specifically, ten organizations stated that their policy is not to reply to surveys. Three claimed they were not interested or had no time, one objected to the methodology, and twelve refused by telephone giving no reason.

III. REVIEW OF THE LITERATURE: SURVEY DESIGN METHODOLOGY

The survey was designed to obtain accurate responses from a reasonably high proportion of potential respondents as cost efficiently as possible, within a limited budget. Several issues related to the selection of procedures for completing this survey have been addressed in the literature. We were not able to find any studies dealing with the topic of biochemical genetic and cytogenetic testing, however. Some of the advice in the literature, and related approaches chosen for this study, are reviewed below.

Method of Administration

Typically, serious studies of elite populations (people high in status, income, or education) employ a personal interview, with open ended questions, for data collection. Generally, however, such studies are concerned with opinions and unusual experiences or perceptions. The literature on elite interviewing, consequently, focuses on the conduct of personal interviews and is of little help in providing guidance for this survey,[2] which was completed by mail with telephone followups.

Most information to be obtained for this study was factual -- whether or not testing had taken place, and if so, what types of testing. Consequently, the function of the elite respondent, the chief executive officer, was to provide impetus for the questionnaire to be completed -- principally by routing it to the appropriate official within his organization. Therefore, a personal interview was not necessarily appropriate. Indeed, the cost of data collection was the principal criterion for selecting a method of administering the instrument. Consequently, a survey by mail was selected as the approach to data collection.

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[2] See, for example, Lewis Anthony Dexter, Elite and Specialized Interviewing (Evanston: Northwestern University Press, 1970).

Obtaining a High Rate of Response

Most of the literature on obtaining high response rates for mail surveys deals with surveys of the general population, and not with surveys of organizations.[3] Nevertheless, some of the principles can be applied to contacts with organizations.

Confidentiality/Anonymity

It is generally believed important to convey to respondents that the information they provide will remain anonymous (as well as to ensure that it does), especially when the topic may be a sensitive one. There were indications that corporations would find this topic of cytogenetic and biochemical testing sensitive.[4] One study suggests that high income respondents are more likely to react favorably to assurances of anonymity than those with low incomes and, consequently, to complete questionnaires.[5] It was decided to protect anonymity by omitting any identifying information on the questionnaire and by asking respondents to send a post card naming their organization and indicating that a questionnaire had been completed.

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[3] See, for example, Don A. Dillman, Mail and Telephone Surveys: The Total Design Method (New York: John Wiley & Sons, 1978).

[4] Articles in the New York Times had contributed to the controversy.

[5] Wesley H. Jones, "Generalizing Mail Survey Inducement Methods: Population Interactions with Anonymity and Sponsorship," Public Opinion Quarterly (POQ), Spring, 1979, p. 108.

There are several pitfalls to this approach that should be noted. First, organizations may return post cards but not questionnaires, and vice versa. (We received 307 post cards and 373 questionnaires; even some of these may not have been matched pairs.) Second, organizations which did not return post cards were contacted by telephone and, in some cases, were re-sent questionnaires if they could not find them. Some of them may have sent in a questionnaire without a post card and later completed and returned a second questionnaire. We have no way to know whether this happened, but believe it occured in only a couple of cases. It is also possible, of course, for questionnaires or post cards to be lost in the mail or lost between the desk of the chief executive officer and the company's mail room.

Questionnaire Design

Instrument design, it has been found, can be important in dealing with sensitive questions in an interview. Although methodological work on this topic generally has dealt with face-to-face interviews of members of the general population, some findings can be applied to this mail survey.[6] There are indications, for example, that whether to report any threatening behavior is not influenced by such factors as question length. Reports on the amount of a behavior, however, seem to be affected by availability of open-ended response categories and the opportunity for the respondent to explain an answer. Several questions in the survey were constructed to allow respondents to explain or qualify their answers.

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[6] Norman M. Bradburn, et al., Improving Interview Method and Questionnaire Design (San Francisco, Jossey-Bass Publishers, 1980), pp. 18-25.

Importance Factor

The literature suggests that the more important the survey is perceived to be by the respondent, the more likely (s)he is to complete a questionnaire.[7] Several methods were used in this survey to convey a sense of importance to respondents. Sponsorship of the study by the U.S. Congress was emphasized, along with the possibility that hearings would be held. The letter from OTA was individually addressed and signed by the Director. The questionnaire was printed on a folded sheet of paper rather than xeroxed on separate pages. As noted, some questionnaires were sent by Federal Express and others by first class mail; both mailing methods indicate that the communication is important. As shown below, however, the Federal Express mailing may have conveyed a greater sense of importance than we ultimately needed. Finally, during telephone followups, the caller once again conveyed the urgent need for responses to the questionnaire.

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[7] See, for example Kent L. Tedin and C. Richard Hofstetter, "The Effect of Cost and Importance Factors on the Return Rate for Single and Multiple Mailings," Public Opinion Quarterly, Spring, 1982, pp. 122-127.

IV. RESULTS

Response Patterns

It is not easy to gain the attention of the chief executive officers of major corporations with a questionnaire, especially when many of them report receiving hundreds a year and have established corporate policies of not responding. Table 1 shows the cumulative totals of post cards received by the end of each weekly time period during the main survey. Separate rates are shown for organizations which received Federal Express versus first class mailings. In Table 2, organizations also are listed according to whether they are among the two hundred largest or three hundred smallest of the corporations, or whether they are utilities or unions.

It can be seen from Table 1 that organizations that received the questionnaire by Federal Express held a lead in the post card returns throughout the survey period, but the size of the lead diminished significantly after the first week. By the end of week 10, 52.9% of the 293 postcards received had been returned by organizations which had received a Federal Express mailing; 47% of those returning post cards had received a first class mailing. The small difference in rates of return suggests to NORC that Federal Express was not a particularly cost effective method of mailing, given that it cost $1,450 for the Federal Express mailings and only $50 for those sent first class. The seventeen additional cases contributed by the more expensive approach each cost $82 more than the others.

Whether better rates of response were obtained from larger or smaller companies is of interest. It should be remembered that all of the 200 largest companies received telephone followups, whereas companies in the bottom 300 were recontacted only if they belonged to a key industry group. Table 2 shows that, prior to week 3, when telephone follow-ups began, approximately 33% of the largest organizations had returned post cards, whereas 28% of the smallest organizations had done so. Over time, the lead of the largest corporations increased, suggesting that the impact of follow-up activities was greatest for this group, as it should have been. Of course, other factors as well may have contributed to the higher response rate of larger companies. The response rate for utilities was relatively high, at 68%, and for unions low, at 36%.

Response Quality

Coverage

Generally, those responding to the questionnaire with whom we talked on the telephone attempted to locate someone within the company with the expertise to answer the questions. Some organizations in the Fortune 500 are holding companies,[7] owning subsidiary organizations that operate autonomously. Some organizations refused to respond because they were unable to devote resources to contacting their subsidiaries to ask about testing. Others either answered to the best of their knowledge or made efforts to contact their subsidiaries. We have no knowledge about the level of effort employed in completing each questionnaire.

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[7] Fortune includes holding companies in their listings if more than 50% of revenues are from manufacturing or mining.

Missing Data

A limitation of an anonymous questionnaire is that it is not possible to contact the respondent about missing information or unclear responses. Generally, the proportions of cases missing information on any particular item was low. On questions 1-6, approximately 3% of respondents failed to answer each item, generally by leaving it blank. Eight questionnaires (2%) did not include enough information so that the company could be classified as a corporation or utility.

Table 1

POST CARDS RECEIVED BY WEEK, BY TYPE OF MAILING,
(MAIN SURVEY ONLY)

	Time Period																			
	Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		Week 7		Week 8		Week 9		Week 10	
	3/31 - 4/6		4/7 - 4/13		4/14 - 4/20		4/21 - 4/27		4/28 - 5/4		5/5 - 5/11		5/12 - 5/18		5/19 - 5/25		5/26 - 6/1		6/2 - 6/8	
			Cumul.		Cumul.		Cumul.		Cumul.		Cumul.		Cumul.		Cumul.		Cumul.		Cumul.	
	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
Post Cards:	102	-	171	-	219	-	234	-	245	-	256	-	266	-	275	-	279	-	293	-
Type of Mailing:																				
Federal Express	68	66.7	96	56.0	118	53.8	124	53.0	128	52.0	134	52.3	138	52.0	146	53.0	148	53.0	155	52.9
First Class	34	32.4	75	43.4	101	46.1	110	47.0	117	48.0	122	48.0	128	48.0	129	47.0	131	47.0	138	47.0

TABLE 2

POST CARDS RECEIVED BY ORGANIZATION SIZE AND TYPE

Time Period

	Week 1 3/31 - 4/6		Week 2 4/7 - 4/13		Week 3 4/14 - 4/20		Week 4 4/21 - 4/27		Week 5 4/28 - 5/4		Week 6 5/5 - 5/11		Week 7 5/12 - 5/18		Week 8 5/19 - 5/25		Week 9 5/26 - 6/1		Week 10 6/2 - 6/8	
	Number	%	Cumul. Number	%	Cumul. Number	%	Cumul. Number	%	Cumul. Number	%	Cumul. Number	%	Cumul. Number	%	Cumul. Number	%	Cumul. Number	%	Cumul. Number	%
Post Cards:	102	-	171	-	219	-	234	-	245	-	256	-	266	-	275	-	279	-	293	-
Organization Size/ Type:																				
Corporations																				
Top 200	34	17.0	65	32.5	84	42.0	91	46.0	97	49.0	103	51.0	109	55.0	114	57.0	117	58.5	123	61.5
Bottom 300	53	17.6	84	28.0	100	33.0	107	36.0	112	37.0	117	39.0	121	40.0	124	41.0	124	41.0	132	44.0
Utilities	14	28.0	19	38.0	31	62.0	32	64.0	32	64.0	32	64.0	32	64.0	33	66.0	34	68.0	34	68.0
Unions	1	9.0	3	27.0	4	36.0	4	36.0	4	36.0	4	36.0	4	36.0	4	36.0	4	36.0	4	36.0
Totals	102	19.0%	171	31.97%	219	40.9%	234	43.7%	245	45.7%	256	57.8%	266	49.7%	275	51.4%	279	52.1%	293	54.8%

Testing: Overall Rates

The following tables summarize the answers to the various questions on testing. Percentages are based on the total number of responses included in the analysis: 366. The questionnaire contains the precise phrasing of each question.

Few organizations report current biochemical genetic or cytogenetic testing; slightly more have conducted any such tests in the past twelve years; still more anticipate at least a possibility of conducting such tests in the future. Organizations were instructed on the questionnaire to include in their answers any instances of testing, so that positive responses can include isolated instances of testing as well as long term testing programs. Table 3 summarizes these results by type of organization, main industrial classification, and according to industrial group.[8] Among the six organizations currently testing (1.6%), two of them are engaged in the chemical industry as their principal activity. Two others are utilities, and the other two are in the electronics industry.

Seventeen organizations (4.6%) have tested in the past. Half of these are in the chemical industry. Of those organizations that have tested in the past twelve years, five are still testing today. Only one organization reports current testing but no testing in the past twelve years.

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[8] Each organization was rated according to the first industrial group into which it classified itself and then according to other industrial categories listed, up to three. The table shows testing by main (first) industrial category and, in parentheses, any representation in that industry.

Table 3

TESTING: CURRENT, PAST AND FUTURE TESTERS BY ORGANIZATION TYPE AND MAIN INDUSTRY

	Current Testing	Past Testing	Future Testing	No Testing
	N = 6	N = 17	N = 59	N = 244
Organization type:				
Corporations	4	16	49	234
Unions	0	0	0	5
Utilities	2	1	9	5
Other	–	–	1	0
Main Industry:				
Chemicals	2	8	11	14
Utilities	2	1	10	5
Petroleum	0	0	4	26
Pharmaceuticals	0	0	3	8
Rubbers, Plastics	0	0	3	1
Metals	0	0	2	22
All others (any others)	2	8	26	244
Total	6 (1.8%)	17 (5.2%)	59 (18.1%)	244 (74.8%)

Fifty-nine organizations (16.1%) may test in the future, they report.

More animal testing is conducted than testing in the workplace, according to answers to question 18 on whether the organization ever has conducted test on animals. Twenty-four organizations report testing on animals for chromosomal aberrations; ten have tested for genetic predisposition to harmful effects from chemicals. Of those testing on animals, five have ever tested on humans. (See Table 4.)

Table 4

ANIMAL TESTING, BY EVER TESTED IN WORKPLACE

Current or Past Workplace Testing	Animal Test for: Chromosomal aberrations	Animal Test for: Genetic Predisposition
	N = 24	N = 10
No	20	9
Yes	4	1

Types of Testing: Biochemical Genetic and Cytogenetic

Organizations that reported some biochemical genetic testing were asked whether they had ever tested employees for any red blood cell and serum disorders (A), liver detoxification systems (B), immune system markers (C), or heterogygous chromosomal instabilities (D). Within each of these four broad categories A through D, several examples were included. Of those testing, there were fourteen organizations that have tested for red blood cell and serum disorders (category A), three in category B, five in category C and no organizations reporting a test in category D. Those organizations testing in category A frequently have conducted more than one test within this category, such as sickle cell trait, G-6-PD, or SAT. The most frequently used test is that for sickle cell trait, for which ten organizations have tested. G-6-PD and SAT were both the second most frequently used individual tests. (See Table 5 for summary of the frequency of individual biochemical genetic tests.)

For each individual test, companies were asked about the purpose of the testing and the type of employee tested. Testing was usually routine, less often for research purposes, or conducted for other reasons. These other reasons are not specified.

The type of employee chosen for testing was most often based on ethnicity and race for sickle cell testing, and job category for other types of tests. No organization reported basing a test on employees' sex.

Organizations that report having conducted cytogenetic testing were asked whether they had looked for chromosomal aberrations (CA), sister chromatic exchanges (SCE), mutations by assaying the DNA (DNA), mutations by assaying the enzymes (ENZ), or something else. Four organizations have tested for chromosomal aberrations and two for SCE. No one claimed to have tested

Table 5

TYPE OF TESTING BY REASONS TESTED

(N = 18)

	Sickle Cell	G-6-PD	SAT	Methemo-globin	Any A[a]	Any B[a]	Any C[a]	CA	SCE
	Number	Number	Number	Number	Number	Number	Number	Number	Number
Reasons/Types tested:									
(a) Testing routine?	5	3	1	0	1	1	4	1	0
(b) Testing for research?	1	0	2	1	2	1	0	1	2
(c) Other reasons?	6	2	2	1	2	1	3	3	0

Table 6

TYPE OF TESTING BY EMPLOYEED CATEGORY TESTED

(N = 18)

	Sickle Cell	G-6-PD	SAT	Methemo-globin	Any A[a]	Any B[a]	Any C[a]	CA	SCE
2. Testing by:									
(a) Job category?	1	2	2	0	2	1	1	2	1
(b) Ethnicity/race?	7	0	0	0	0	0	0	0	0
(c) Sex?	0	0	0	0	0	0	0	0	0
Total testing	10(2.7%)	4(1.1%)	4(1.1%)	1(.3%)	3(.8%)	2(.5%)	4(1.1%)	4(1.1%)	2(.5%)

[a] Test not specified by company.

[b] Since categories above are not mutually exclusive, total can be less than/more than sum of categories.

for mutations, by assaying either the DNA or the enzymes. CA testing was done for unspecified reasons by three companies; SCE testing was done for research purposes. Job category was the only one of the three employee-related characteristics taken into account in deciding whom to test except for sickle cell. (See Table 6.)

Several questions were asked for each type of testing (biochemical genetic and cytogenetic) about factors considered in decisions to implement testing programs and criteria employed in selecting specific tests. All categories provided received at least one response. Ten responses indicated that data was reviewed either from animal studies or from epidemiologic studies in decisions on whether to perform biochemical genetic testing. In four instances, such reviews were conducted in deciding whether to implement cytogenetic testing. The various cirteria for selecting a particular test were fairly evenly employed, although cost appears to have been less important than the various scientific criteria. (See Table 7 for the distribution of responses.)

Results of Testing

Organizations have taken a considerable range of actions as a result of the biochemical genetic or cytogenetic testing programs they have conducted. The most common action reported is informing an employee of a potential problem. Eight organizations have taken such an action. Five of the categories are related to actions taken to inform the employee or to protect him, ranging from the most minimum such activity - merely informing the employee - to the most extreme, that of discontinuing a product.

Employees were informed in eight instances (out of the 18) and a product was discontinued only once. In seven cases, an employee was either transferred or another job was suggested. The actions taken, by frequency, are listed in Table 8.

Table 7

TYPE OF TESTING BY FACTORS/CRITERIA FOR SELECTING TESTS

	Biochemical genetic	Cytogenetic
	N-17	N-18
Factors in implementing testing	Number	Number
Cost benefit analysis	2	0
Data from animal studies	4	2
Data-epidemiologic studies	6	2
Legal consequences of not testing	3	0
Unions/employee initiative	3	0
Other	4[a]	3[a]
No response	2	0
Criteria for selecting tests		
Predictive value of test	5	1
Sensitivity of test	3	0
Specificity of test	5	1
Scientific consensus	4	2
Cost of test	2	0
Other	4	3[b]
No response	2	1

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[a] Includes reasons related to protecting employees, research findings.

[b] Includes research findings (general).

Table 8

RESULTS OF TESTING

N = 18

Action Type	Number
Informed employee	8
Transferred employee	5
Personal protection devices	3
Other action	3
Suggested other job	2
Engineering controls	2
Implemented research program	1
Discontinued/changed product	1

Comments on the Questionnaire/Postcards

Respondents were encouraged to qualify their responses or to comment on the questionnaire either on the questionnaire itself or on the postcard. Three companies currently testing provided comments on their questionnaires. One of them stated that their . . . "Answers should not be taken to imply any large scale program or problem." Once mentioned testing for pre-placement and as a part of annual physicals.The third uses testing in "continuing health evaluations" of certain employees.

Two former testers offered comments. One claimed that testing had been used at the request of the State health department for a brief period.

Another reported sickle cell testing as part of a "preventive medical program" on certain people of child bearing age.

Seven possible testers made comments. One noted that "what may be done will depend upon demonstrations that indicated procedures have practical utility." Others expressed observations about the potential for testing in their organization.

Comments received on post cards and from organizations which have never tested, and have no plans to test (approximately 37 were received) ranged from statements that the questions were inappropriate to their organizations to beliefs that testing had no proven value. Many questioned the usefulness of the survey. Several organizations felt that the questionnaire could be misleading becuase information was not requested on how much testing was done.

V. CONCLUSIONS

There was great uncertainty at the onset of this study as to whether to expect any cytogenetic or biochemical genetic testing among the major U.S. corporations, unions and utilities. Six organizations, haowerver, did report testing. Of the organizations that tested in the past, only one continues to test, suggesting a tendency for testing to decline. On the other hand, fifty-nine organizations answered "possibly" to the question of whether they anticipated conducting testing in the next five years.

It is interesting to speculate as to why so many organizations may have stated that they "possibly" anticipate conducting testing in the next five years, especially since many organizations have dropped their testing programs. Some may have chosen to hedge their bets -- as a result of the current controversy surrounding the issue, perhaps good reasons for testing, not now apparent to them, may surface. Perhaps, also, some are not aware of the issues surrounding testing and simply do not know whether this topic may some day apply to them.

APPENDIX A[1]

ANALYSIS OF NONRESPONDENTS

The analysis of nonrespondents among the Fortune 500 companies is based upon 193 cases, including 38 companies who sent in anonymous questionnaires but did not send in postcards identifying themselves as respondents.

Geographically, nonrespondents, like respondents, were spread fairly evenly across the country, as shown in Table A-1.

TABLE A-1

LOCATION OF ALL COMPANIES AND NONRESPONDENTS

Region	Nonrespondents		Companies	
	Number	Proportion	Number	Proportion
Northeast	82	42%	215	43%
Southeast	8	4%	30	6%
Central	80	41%	191	38%
Mountain	2	1%	9	2%
West	21	11%	55	11%

The nonrespondents were concentrated in the smaller two hundred companies. This most probably reflects the fact that our follow-up activities focused on the larger three hundred companies, in addition to industries in key industrial groups. The breakdown of nonrespondents by company size is shown in Table A-2.

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[1] This appendix was prepared by Ken Cohen.

TABLE A-2

SIZE OF NONRESPONDINC COMPANIES

Size of Company	Nonrespondents Number	Proportion
Fortune 100	29	15%
Fortune 200-300	62	32%
Fortune 400-500	102	52%

Companies in the combined key code industries (chemicals, petroleum refining, rubber and plastic products, metal manufacturing and pharmaceuticals) had a nonresponce rate of 31%, which is somewhat lower than the overall nonrepsonse rate of 38.6% for the Fortune 500 companies. (Again, these companies were the focus of our follow-up efforts). Otherwise, particular industries did not deviate significantly from the overall rates. The breakdown by industrial type is given in Table A-3.

Conclusion

These tables to not suggest that any particular type of organization was more likely than any other to refuse to respond to the questionnaire.

TABLE A-3

NONRESPONDENTS BY INDUSTRY TYPE

Industry Type	Nonrespondents Number	Nonrespondents Proportion	Total Companies Number	Total Companies Proportion
10 - Mining, Crude Oil	7	3.6%	13	2.6%
20 - Food	23	11.9%	54	10.8%
21 - Tobacco	1	---	4	---
22 - Textile	5	2.5%	13	2.6%
23 - Apparel	5	2.5%	9	1.8%
25 - Furniture	1	---	1	---
26 - Paper, Fiber, Wood	16	8%	30	6%
27 - Publishing, Printing	8	4%	13	2.6%
28 - Chemicals	11	5.7%	40	8%
29 - Petroleum Refining	11	5.7%	41	8%
30 - Rubber, Plastic	2	---	6	1.2%
31 - Leather	1	---	2	---
32 - Glass, Concrete	3	---	16	3.2%
33 - Metal Manufacturing	14	7.2%	38	7.6%
34 - Metal Products	11	5.7%	23	4.6%
36 - Electronics, Appliances	10	5.2%	37	7.4%
37 - Shipbuilding, Railroad & Transport Equipment	4	2%	9	1.8%

			Total Companies	
Industry Type	Number	Proportion	Number	Proportion
38 - Measuring Equipment	4	2%	15	2.6%
40 - Motor vehicles	5	2.5%	19	3.8%
41 - Aerospace	3	---	14	2.8%
43 - Soaps, Cosmetics	3	---	8	1.6%
44 - Office Equipment	3	---	13	2.6%
45 - Industrial & Farm Equipment	23	11.9%	43	8.6%
46 - Jewelry, Silverware	0	---	0	---
47 - Musical Instruments, Toys	3	---	5	1%
48 - Broadcasting, Motion Pictures	3	---	6	1.2%
49 - Beverages	3	---	11	2.2%

Appendix C

Survey Materials

TECHNOLOGY ASSESSMENT BOARD
TED STEVENS, ALASKA, CHAIRMAN
MORRIS K. UDALL, ARIZ., VICE CHAIRMAN
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LARRY WINN, JR., KANS.
CLARENCE E. MILLER, OHIO
COOPER EVANS, IOWA
JOHN H. GIBBONS

Congreſs of the United States
OFFICE OF TECHNOLOGY ASSESSMENT
WASHINGTON, D.C. 20510

JOHN H. GIBBONS
DIRECTOR

March 22, 1982

Dear Mr.

The Committee on Science and Technology of the U.S. House of Representatives has requested this office to carry out a comprehensive study of the policy issues arising from potential occupational genetic testing. The Committee expects the study to provide the Congress with full and fair information on a complex and sensitive topic. A crucial component of our study will be information and advice from leading U.S. corporations. Since your company is a world leader in many areas relevant to the study, we believe it is extremely important for us to benefit from any experience you may have with such testing programs.

The Office of Technology Assessment (OTA) is a nonpartisan congressional agency that assists the Congress in dealing with complex technical issues. OTA is governed by a bipartisan Congressional board composed of six Representatives and six Senators. A council of ten members eminent in science, technology, and education serves in an advisory capacity. This study is also being assisted by an advisory panel of experts in genetics, occupational medicine, law, and policy from industry, labor, and academia. A list of advisory panel members and their affiliations is enclosed.

We have asked the National Opinion Research Center of the University of Chicago (NORC) to assist OTA by collecting and processing data via a questionnaire. The data will be presented to OTA in aggregate form only, and the raw data will be destroyed.

NORC's brief questionnaire is attached. We believe it will be most helpful if you direct it to your chief executive for health affairs. We respectfully request a response to the questionnaire as soon as possible and are prepared to share the results of the analysis with you when it is completed.

If you have any questions about the study or about OTA, please feel free to contact me at (202) 224-3695, or Geoffrey M. Karny, OTA project director, at (202) 226-2090. Cynthia Thomas, NORC project director, can be contacted about the survey at (212) 971-8200.

Sincerely,

Jack Gibbons

John H. Gibbons

NORC
National Opinion Research Center
University of Chicago
461 Eighth Avenue New York, N.Y. 10001 212/971-8200

March 23, 1982

As one of the leading corporations in this country, your organization has been selected to participate in an important survey we are conducting for the Office of Technology Assessment (OTA) of the United States Congress on the state-of-the-art of genetic and cytogenetic testing programs. The enclosed letter from the OTA describes this study in more detail.

The National Opinion Research Center (NORC) is a not-for-profit academic research corporation affiliated with the University of Chicago. The oldest survey research facility established to do social research in the public interest, NORC has conducted over a thousand studies since its founding in 1941, and has developed careful and systematic methods for ensuring confidentiality. Names are never associated with responses to questions, and data collected are used only for statistical purposes.

It is very important that you complete the enclosed brief questionnaire as soon as possible. Your answers to the questions should include any instance of testing in your corporation, or in any of your subsidiary companies.

To ensure confidentiality, the questionnaire carries no identifying information. Please mail the completed questionnaire in the prepaid NORC envelope. Then, complete and mail the enclosed prepaid post-card. This will inform us that you have participated in the survey by completing a questionnaire.

If you have any questions about the questionnaire, please feel free to telephone me at (212) 971-8200.

Thank you very much.

Sincerely yours,

Cynthia Thomas

Cynthia Thomas
Project Director

NORC/4354 3/82

WORKPLACE SURVEY

INSTRUCTIONS FOR COMPLETING THE QUESTIONNAIRE

The questions concern biochemical genetic and/or cytogenetic testing that may have been conducted by your company on one or more employees or potential employees. By conduct we mean do, contract for, or arrange for. By biochemical genetic tests we mean tests which screen healthy, asymptomatic individuals for the particular genetic traits listed in question 7, and not standard blood chemistry tests or tests used solely for diagnosis. Cytogenetic tests are intended to detect chromosomal aberrations or sister chromatid exchanges.

Do not sign the questionnaire or record any identifying information on it. Answers should include any instances of testing in your corporation.

Please return the questionnaire to NORC before April 12.

---

1. Is your company **currently** conducting biochemical genetic testing of employees or potential employees? Yes ☐ No ☐

---

2. Has your company conducted any biochemical genetic testing of employees or potential employees in the **past twelve years?** Yes ☐ No ☐

---

3. Does your company anticipate conducting biochemical genetic testing in the **next five years?** Yes ☐ No ☐ Possibly ☐

---

4. Is your company **currently** conducting cytogenetic testing of employees or potential employees? Yes ☐ No ☐

---

5. Has your company conducted any cytogenetic testing of employees or potential employees in the **past twelve years?** Yes ☐ No ☐

---

6. Does your company anticipate conducting cytogenetic testing during the **next five years?** Yes ☐ No ☐ Possibly ☐

IF YOUR COMPANY NEVER HAS DONE EITHER BIOCHEMICAL GENETIC OR CYTOGENETIC TESTING, SKIP TO QUESTION 18.

IF BIOCHEMICAL GENETIC TESTING HAS EVER BEEN DONE, PLEASE ANSWER QUESTIONS 7-11. IF NOT, PLEASE SKIP TO Q. 12.

7. Has your company tested workers for . . .	Yes	No
A. any red blood cell and serum disorders, including sickle cell trait, glucose-6-phosphate dehydrogenase deficiency (G-6-PD), methemoglobin reductase deficiency, serum alpha-1-antitrypsin deficiency (SAT), alpha and beta thalassemias?	☐	☐
B. any liver detoxification systems, including aryl hydrocarbon hydroxylase inducibility (AHH), slow vs fast acetylation?	☐	☐
C. any immune system markers, including allergic respiratory disease, contact dermatitis, histocompatibility markers (HLA)?	☐	☐
D. any heterozygous chromosomal instabilities, including Bloom syndrome, Fanconi syndrome, ataxia-telangiectasia, xeroderma pigmentosum?	☐	☐

ENTER BELOW NAME OF EACH SPECIFIC CONDITION TESTED FOR (e.g., G-6-PD). ANSWER QUESTIONS 8 & 9 FOR EACH. IF MORE THAN 4 CONDITIONS, RECORD ON ADDITIONAL SHEET OF PAPER.

ENTER SPECIFIC CONDITION NAME HERE---->								
	Yes	No	Yes	No	Yes	No	Yes	No
8. Was testing done . . . a) routinely (e.g., yearly) or during regular specified circumstances?	☐	☐	☐	☐	☐	☐	☐	☐
b) for research purposes (e.g., hypothesis testing)?	☐	☐	☐	☐	☐	☐	☐	☐
c) for any other reasons?	☐	☐	☐	☐	☐	☐	☐	☐
9. Was testing to detect increased risk of disease ever based on an employee's . . . a) job category?	☐	☐	☐	☐	☐	☐	☐	☐
b) sex?	☐	☐	☐	☐	☐	☐	☐	☐
c) ethnic or racial background?	☐	☐	☐	☐	☐	☐	☐	☐

10. What factors have been considered in decisions to implement any biochemical genetic testing programs?

A. Cost benefit analysis ☐
B. Data suggesting a possible association between chemical exposure and illness in animal studies ☐
C. Data suggesting a possible association between chemical exposure and illness in epidemiologic studies ☐
D. Legal consequences of failure to test ☐
E. Union/employee initiative ☐
F. Something else. What? ________________ ☐

---

11. What criteria were employed in the choice of a specific test?

A. Predictive value of the test ☐
B. Sensitivity of the test ☐
C. Specificity of the test ☐
D. Scientific consensus ☐
E. Cost of the test ☐
F. Something else. What? ☐

IF CYTOGENETIC TESTING HAS EVER BEEN DONE, PLEASE ANSWER QUESTIONS 12-16. IF NOT, PLEASE SKIP TO Q. 18.

12. Has your company tested workers for exposure to chemicals by looking for . . .

	Yes	No
A. chromosomal aberrations	☐	☐
B. sister chromatid exchanges (SCE)	☐	☐
C. mutations by assaying the DNA	☐	☐
D. mutations by assaying the enzymes	☐	☐
E. something else? What? ____________	☐	☐

ENTER BELOW NAME OF EACH SPECIFIC CONDITION TESTED FOR (e.g., SCE). ANSWER QUESTIONS 13 & 14 FOR EACH. IF MORE THAN CONDITIONS, RECORD ON ADDITIONAL SHEET OF PAPER.

ENTER SPECIFIC CONDITION NAME HERE---->								
	Yes	No	Yes	No	Yes	No	Yes	No
13. Was testing done . . . a) routinely (e.g., yearly) or during regular specified circumstances?	☐	☐	☐	☐	☐	☐	☐	☐
b) for research purposes (e.g., hypothesis testing)?	☐	☐	☐	☐	☐	☐	☐	☐
c) for any other reasons?	☐	☐	☐	☐	☐	☐	☐	☐
14. Was testing to detect increased risk of disease ever based on an employee's. . . a) job category?	☐	☐	☐	☐	☐	☐	☐	☐
b) sex?	☐	☐	☐	☐	☐	☐	☐	☐
c) ethnic or racial background?	☐	☐	☐	☐	☐	☐	☐	☐

15. What factors have been considered in decisions to implement any cytogenetic testing programs?

- A. Cost benefit analysis ☐
- B. Data suggesting a possible association between chemical exposure and illness in animal studies ☐
- C. Data suggesting a possible association between chemical exposure and illness in epidemiologic studies ☐
- D. Legal consequences of failure to test ☐
- E. Union/employee initiative ☐
- F. Something else. What? ____________ ☐

16. What criteria were employed in the choice of a specific test?

- A. Predictive value of the test ☐
- B. Sensitivity of the test ☐
- C. Specificity of the test ☐
- D. Scientific consensus ☐
- E. Cost of the test ☐
- F. Something else. What? ☐ ____________

17. Which actions has your company ever taken as a result of biochemical genetic or cytogenetic testing?

A. Informed employee of a potential problem ☐

B. Suggested employee seek job elsewhere ☐

C. Placed an employee or transferred an employee to a different job in the company ☐

D. Implemented engineering controls ☐

E. Recommended personal protection devices ☐

F. Implemented a research program ☐

G. Discontinued a product or changed materials in a product ☐

H. Some other action. What? ☐

____

---

18. Has your company ever conducted any testing on whole animals or their cultured cells for . . .

	Yes	No
A. chromosomal aberrations or sister chromatid exchanges as a result of exposure to workplace chemicals?	☐	☐
B. genetic predisposition to harmful effects from exposure to workplace chemicals?	☐	☐

---

19. What is the major industrial classification of your company (such as chemicals, food or textiles)?

---

20. Please use this space for your comments, if any, about these questions.

Thank you for completing this questionnaire. The information you have provided will be held in strict confidence. Data will be made available to Congress in statistical form only.

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TECHNOLOGY ASSESSMENT BOARD
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JOHN H. GIBBONS

Congreſs of the United States
OFFICE OF TECHNOLOGY ASSESSMENT
WASHINGTON, D.C. 20510

JOHN H. GIBBONS
DIRECTOR

March 22, 1982

Dear Mr.

The Committee on Science and Technology of the U.S. House of Representatives has requested this office to carry out a comprehensive study of the policy issues arising from potential occupational genetic testing. The Committee expects the study to provide the Congress with full and fair information on a complex and sensitive topic. A crucial component of our study will be information and advice from leading U.S. labor organizations. Since your union is a world leader in many areas relevant to the study, we believe it is extremely important for us to benefit from any experience you may have with such testing programs.

The Office of Technology Assessment (OTA) is a nonpartisan congressional agency that assists the Congress in dealing with complex technical issues. OTA is governed by a bipartisan Congressional board composed of six Representatives and six Senators. A council of ten members eminent in science, technology, and education serves in an advisory capacity. This study is also being assisted by an advisory panel of experts in genetics, occupational medicine, law, and policy from industry, labor, and academia. A list of advisory panel members and their affiliations is enclosed.

We have asked the National Opinion Research Center of the University of Chicago (NORC) to assist OTA by collecting and processing data via a questionnaire. The data will be presented to OTA in aggregate form only, and the raw data will be destroyed.

NORC's brief questionnaire is attached. We believe it will be most helpful if you direct it to your director for health and safety. We respectfully request a response to the questionnaire as soon as possible and are prepared to share the results of the analysis with you when it is completed.

If you have any questions about the study or about OTA, please feel free to contact me at (202) 224-3695, or Geoffrey M. Karny, OTA project director, at (202) 226-2090. Cynthia Thomas, NORC project director, can be contacted about the survey at (212) 971-8200.

Sincerely,

John H. Gibbons

John H. Gibbons

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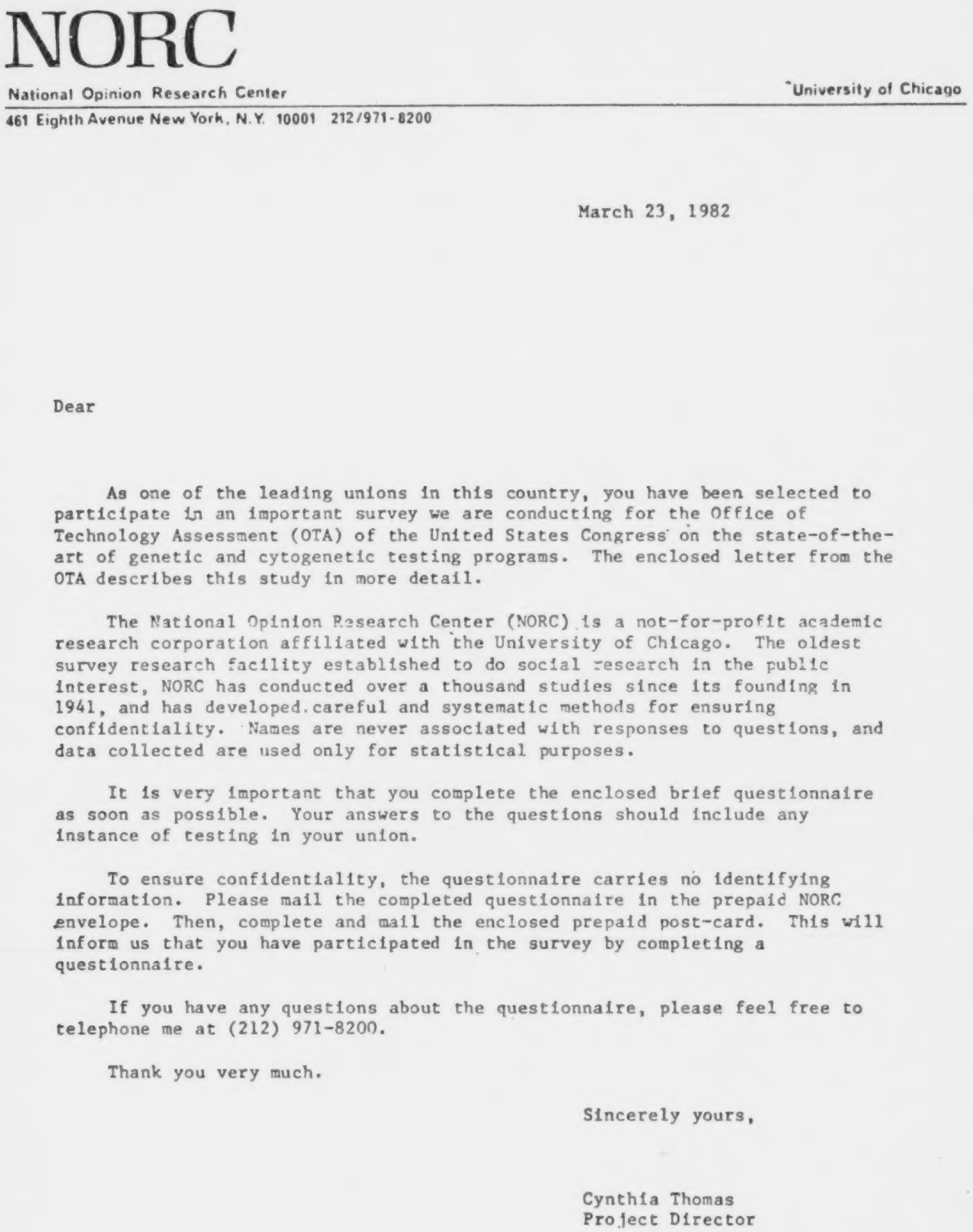

NORC
National Opinion Research Center
University of Chicago
461 Eighth Avenue New York, N.Y. 10001 212/971-8200

March 23, 1982

Dear

As one of the leading unions in this country, you have been selected to participate in an important survey we are conducting for the Office of Technology Assessment (OTA) of the United States Congress on the state-of-the-art of genetic and cytogenetic testing programs. The enclosed letter from the OTA describes this study in more detail.

The National Opinion Research Center (NORC) is a not-for-profit academic research corporation affiliated with the University of Chicago. The oldest survey research facility established to do social research in the public interest, NORC has conducted over a thousand studies since its founding in 1941, and has developed careful and systematic methods for ensuring confidentiality. Names are never associated with responses to questions, and data collected are used only for statistical purposes.

It is very important that you complete the enclosed brief questionnaire as soon as possible. Your answers to the questions should include any instance of testing in your union.

To ensure confidentiality, the questionnaire carries no identifying information. Please mail the completed questionnaire in the prepaid NORC envelope. Then, complete and mail the enclosed prepaid post-card. This will inform us that you have participated in the survey by completing a questionnaire.

If you have any questions about the questionnaire, please feel free to telephone me at (212) 971-8200.

Thank you very much.

Sincerely yours,

Cynthia Thomas
Project Director

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NORC/4354 3/82

WORKPLACE SURVEY

INSTRUCTIONS FOR COMPLETING THE QUESTIONNAIRE

The questions concern biochemical genetic and/or cytogenetic testing that may have been conducted by your union on one or more union members or potential members. By conduct we mean do, contract for, or arrange for. By biochemical genetic tests we mean tests which screen healthy, asymptomatic individuals for the particular genetic traits listed in question 7, and not standard blood chemistry tests or tests used solely for diagnosis. Cytogenetic tests detect chromosomal aberrations or sister chromatid exchanges.

Do not sign the questionnaire or record any identifying information on it. Answers should include any instances of testing in your union.

Please return the questionnaire to NORC before April 12.

---

1. Is your union **currently** conducting biochemical genetic testing of members or potential members? Yes ☐ No ☐

2. Has your union conducted any biochemical genetic testing of members or potential members in the **past twelve years?** Yes ☐ No ☐

3. Does your union anticipate conducting biochemical genetic testing in the **next five years?** Yes ☐ No ☐ Possibly ☐

4. Is your union **currently** conducting cytogenetic testing of members or potential members? Yes ☐ No ☐

5. Has your union conducted any cytogenetic testing of members or potential members in the **past twelve years?** Yes ☐ No ☐

6. Does your union anticipate conducting cytogenetic testing during the **next five years?** Yes ☐ No ☐ Possibly ☐

IF YOUR UNION NEVER HAS DONE EITHER BIOCHEMICAL GENETIC OR CYTOGENETIC TESTING, SKIP TO QUESTION 18.

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IF BIOCHEMICAL GENETIC TESTING HAS EVER BEEN DONE, PLEASE ANSWER QUESTIONS 7-11. IF NOT, PLEASE SKIP TO Q. 12.

7. Has your union tested members for . . .	Yes	No
A. any **red blood cell and serum disorders**, including sickle cell trait, glucose-6-phosphate dehydrogenase deficiency (G-6-PD), methemoglobin reductase deficiency, serum alpha-1-antitrypsin deficiency (SAT), alpha and beta thalassemias?	☐	☐
B. any **liver detoxification systems**, including aryl hydrocarbon hydroxylase inducibility (AHH), slow vs fast acetylation?	☐	☐
C. any **immune system markers** including allergic respiratory disease, contact dermatitis, histocompatibility markers (HLA)?	☐	☐
D. any **heterozygous chromosomal instabilities** including Bloom syndrome, Fanconi syndrome, ataxia-telangiectasia, xeroderma pigmentosum?	☐	☐

ENTER BELOW NAME OF EACH SPECIFIC CONDITION TESTED FOR (e.g., G-6-PD). ANSWER QUESTIONS 8 & 9 FOR EACH. IF MORE THAN 4 CONDITIONS, RECORD ON ADDITIONAL SHEET OF PAPER.

ENTER SPECIFIC CONDITION NAME HERE——>								
	Yes	No	Yes	No	Yes	No	Yes	No
8. Was testing done . . .								
a) routinely (e.g., yearly) or during regular specified circumstances?	☐	☐	☐	☐	☐	☐	☐	☐
b) for research purposes (e.g., hypothesis testing)?	☐	☐	☐	☐	☐	☐	☐	☐
c) for any other reasons?	☐	☐	☐	☐	☐	☐	☐	☐
9. Was testing to detect increased risk of disease ever based on a member's . . .								
a) job category?	☐	☐	☐	☐	☐	☐	☐	☐
b) sex?	☐	☐	☐	☐	☐	☐	☐	☐
c) ethnic or racial background?	☐	☐	☐	☐	☐	☐	☐	☐

10. What factors have been considered in decisions to implement any biochemical genetic testing programs?

A. Cost benefit analysis ☐
B. Data suggesting a possible association between chemical exposure and illness in animal studies ☐
C. Data suggesting a possible association between chemical exposure and illness in epidemiologic studies ☐
D. Legal consequences of failure to test ☐
E. Union member initiative ☐
F. Something else. What? ____________ ☐

11. What criteria were employed in the choice of a specific test?

A. Predictive value of the test ☐
B. Sensitivity of the test ☐
C. Specificity of the test ☐
D. Scientific consensus ☐
E. Cost of the test ☐
F. Something else. What? ☐
____

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IF CYTOGENETIC TESTING HAS EVER BEEN DONE, PLEASE ANSWER QUESTIONS 12-16. IF NOT, PLEASE SKIP TO Q. 18.

12. Has your union tested members for exposure to chemicals by looking for . . .

	Yes	No
A. chromosomal aberrations	☐	☐
B. sister chromatid exchanges (SCE)	☐	☐
C. mutations by assaying the DNA	☐	☐
D. mutations by assaying the enzymes	☐	☐
E. something else? What? ________________	☐	☐

ENTER BELOW NAME OF EACH SPECIFIC CONDITION TESTED FOR (e.g., SCE). ANSWER QUESTIONS 13 & 14 FOR EACH. IF MORE THAN 4 CONDITIONS, RECORD ON ADDITIONAL SHEET OF PAPER.

ENTER SPECIFIC CONDITION NAME HERE——>								
	Yes	No	Yes	No	Yes	No	Yes	No
13. Was testing done . . . a) routinely (e.g., yearly) or during regular specified circumstances?	☐	☐	☐	☐	☐	☐	☐	☐
b) for research purposes (e.g., hypothesis testing)?	☐	☐	☐	☐	☐	☐	☐	☐
c) for any other reasons?	☐	☐	☐	☐	☐	☐	☐	☐
14. Was testing to detect increased risk of disease ever based on a member's . . . a) job category?	☐	☐	☐	☐	☐	☐	☐	☐
b) sex?	☐	☐	☐	☐	☐	☐	☐	☐
c) ethnic or racial background?	☐	☐	☐	☐	☐	☐	☐	☐

15. What factors have been considered in decisions to implement any cytogenetic testing programs?

- A. Cost benefit analysis ☐
- B. Data suggesting a possible association between chemical exposure and illness in animal studies ☐
- C. Data suggesting a possible association between chemical exposure and illness in epidemiologic studies ☐
- D. Legal consequences of failure to test ☐
- E. Union member initiative ☐
- .. Something else. What? ________________ ☐

16. What criteria were employed in the choice of a specific test?

- A. Predictive value of the test ☐
- B. Sensitivity of the test ☐
- C. Specificity of the test ☐
- D. Scientific consensus ☐
- E. Cost of the test ☐
- F. Something else. What? ☐ ________________

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17. Which actions has your union ever taken as a result of biochemical genetic or cytogenetic testing?

.. Informed member of a potential problem ☐

. Suggested member seek job elsewhere ☐

. Suggested member seek transfer to a different job in the corporation ☐

. Recommended corporation implement engineering controls ☐

. Recommended corporation provide personal protection devices ☐

F. Recommended corporation implement a research program ☐

G. Recommended corporation discontinue a product or change materials in a product ☐

H. Implemented our own research program ☐

I. Negotiated items C,D, E or F in a health/safety contract ☐

J. Some other action. What? ☐

____

8. Has your union ever conducted any testing on whole animals or their cultured cells for . . .	Yes	No
A. chromosomal aberrations or sister chromatid exchanges as a result of exposure to workplace chemicals?	☐	☐
B. genetic predisposition to harmful effects from exposure to workplace chemicals?	☐	☐

9. What are the major industrial classifications (such as chemical, food, or textiles) of those companies in the Fortune 500 in which your members work?

0. Please use this space for your comments, if any, about these questions.

ank you for completing this questionnaire. The information you have provided will be held in rict confidence. Data will be made available to Congress in statistical form only.

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OCCUPATIONAL GENETIC TESTING ADVISORY PANEL

Arthur D. Bloom, M.D., Chair
Professor of Pediatrics
Director of Clinical Genetics
and Development
Columbia University

J. Grant Brewen, Ph.D.
Director
Molecular and Applied Genetics
Laboratory
Allied Chemical Corporation

Eula Bingham, Ph.D.
Professor, Environmental Health
University of Cincinnati
Former Director, OSHA

Patricia Buffler, Ph.D.
Associate Dean for Research
and Associate Professor of
Epidemiology
University of Texas
School of Public Health

Ira Cisin, Ph.D.
Director, Social Research Group
George Washington University

Burford W. Culpepper, M.D.
Assistant Director, Medical
Division
E. I. DuPont de Nemours & Company

James D. English
Associate General Counsel
United Steel Workers of America

Neil Holtzman, M.D.
Associate Professor of Pediatrics
Johns Hopkins University

Paul Kotin, M.D.
Consultant
Former Medical Director
Johns-Manville Corporation

Thomas O. McGarity
Professor of Law
University of Texas at Austin

Rafael Moure, Ph.D.
Industrial Hygienist
Oil Chemical & Atomic Workers Union

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Chief, Division of Medical Genetics
Howard University
College of Medicine

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Senior Program Officer
Institute of Medicine
National Academy of Sciences

Gilbert Omenn, M.D., Ph.D.
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The Brookings Institution

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for Occupational and Environmental Health
University of Utah

Stuart Schweitzer, Ph.D.
Professor and Director
Program in Health Planning
and Policy Analysis
UCLA School of Public Health

Robert Veatch, Ph.D.
Professor, Medical Ethics
The Kennedy Institute of Ethics
Georgetown University

Respondent Comments About Survey

Respondents were asked to comment about any aspect of the survey or questionnaire in a space provided on the questionnaire and one the postcard. The following list comprises the totality of comments received from the respondents. They have been grouped by status of tester: Current Tester, Past Tester, Future Testers with prior testing experience, and No Testing (Past, Present, Future), Information contained at the end of a quote is descriptive information about the respondent provided by the contractor. In cases where a number of appears, it is the Standard Industrial Classification (SIC) Code as given by the respondent. The quotes are printed as written by respondent. No editing has been done.

Comments by present testers

"Answers should not be taken to imply apy large scale program or problem. Medical/Ind Hygiene depts have done 'common sense' preventive sampling and testing to reassure employees in specific small areas of company where even low level risk might occur"

-presently biochemical genetic testing and past biochemical genetic testing

"We do a chemical profile (blood test) that tests 20 different factors (sic) in the blood and CBC as a matter of course for pre-placement and annual physical."

-presently biochemical genetic testing and past biochemical genetic testing

"Cytogenetic testing is one aspect of continuing health evaluations on personnel engaged in "hands on" maintenance work in 500 KV electric transmission lines."

-presently cytogenetic testing and past cytogenetic testing

Comments by past testers

"Sickle cell trait testing was offered as a service to employees for a brief period at the request of the state health department. It was never used as a screening procedure in relation to the job."

-past biochemical genetic testing

"Only testing has been for sickle trait or mediterranean anemia trait in a few people of child bearing age as part of preventive medical program not consistently".

-past biochemical genetic testing

Comments by companies that anticipate future testing, but have not conducted any testing to date:

"Company supports research activities relevant to No. 18 through trade associations and CIIT."

"Such tests as described in 18A are run on materials and products routinely as part of an overall safety assessment."

"Some essential questions have been omitted--namely,

1. are materials being used with chromosomal and/or genetic harmful effects?

2. is there clinical evidence or even suspicion to justify performing such tests? (in a given workplace)

3. are tests results indicators (valid and reliable) of actual or potential health risks to employees?"

"18A, "Chromosomal aberrations" may be included in a mutagenic screen on chemicals or as a followup to mutagenic testing."

"It is conceivable we may wish to initiate a limited project of cytogenetic or biochemical genetic testing in employees "exposed" to nuclear radiation in next 5-10 years. Our stringent monitoring controls on radiation exposure may not result in this requirement. However, it is just a possibility."

"What may be done (#3 and #6) will depend upon demonstration that indicated procedures have practical utility."

FROM A UNION QUESTIONNAIRE: "(NAME DELECTED BY NORC) Plant may have been cytogenetic testing by company for which they worked benzene (sic)"

Comments from companies not now, previously, or in the future planning to test.

" ---- Inc. is a multifacility manufacturing co. that is not involved in genetic testing." (540, aircraft)

"We do not perform health testing for the specific purpose of detecting genetic or cytogenetic health effects of occupational exposure to chemicals. We have not conducted this type of health testing since we have not identified chemicals to which our employees are exposed that could potentially cause these genetic health problems." (563, electric utility)

"I really wonder if the value of this project will compare favorably with the cost of it - our federal budget deficit is large and we have operated in the red for decades - this looks like the sort of expenditure the USA could get along without!" (547, cement and construction materials)

"Not needed. Virtually no chemical exposure. Operations are light assembly of prefinished parts of materials". (612, recreational vehicles)

"Totally out of context with the nature of our business." (613, electronic equipment)

"Does not seem relative to our business". (616, gas and oil production)

"The need or cause for such testing has never been revealed". (617, cement)

"Our company presently has done noise level testing at all facilities and "Blood-Lead Chemistry" and "Chest X-ray" testing of all employees working in painting rooms on an annual basis". (618, Hand tools)

"Privacy of individual employees should not be imposed upon unless there is a clear indication from Public Health authorities that program is warranted and public is informed in a manner that would educate employees on the need for it." (619, books and journals)

"We have no information that any products we produce require any such testing". (620, refractories and building materials)

"Company maintains minimal risk environments [through] selective and controlled use of chemical and physical agents in conjunction with continuing industrial hygiene appraisals". (622, cross linked plastics)

"Ref. Question #18: The American Petroleum Institute acting on behalf of the industry, is engaged in a major, on-going program of animal testing. Generic petroleum products are employed in this toxicology testing program which includes genetic considerations." (286, chemicals)

"We are computer and word processing system manufacturers and are not involved in chemical or genetic work." (292)

"Thank you for sending questionnaire. However, it does not seem relevant to our business or to our future plans." (219, flat glass, fluid system components, plastic products)

FROM A UNION QUESTIONNAIRE: "Union never conducted tests. Company screening often by union demand has been limited to clinical tests and biological monitoring, no cytogenetic or biochemical genetic tests". (103, union)

"We have conducted and continue to conduct chemical exposure testing on whole animals and their cultured cells for chromosomal aberrations and sister chromatid exchanges. This is sometimes done as one part of our toxicological evaluations conducted to enable the proper planning and management which assures safe handling and usage of intermediate and product materials." (453, petroleum products and petrochemicals)

"We have used these tests as screening procedures in animals. We do not find them sufficiently validated for use on our employees, or prospective employees." (478, petrochemicals)

"In our opinion none of our industrial operations are associated with environmental hazards which indicate any employee health benefit from either biochemical genetic or cytogenetic testing." (479, mining, smelting)

"We believe cytogenic (sic) testing methodology to screen human populations rquires further standardization and validation before we would consider using it in our employee population. As a general principle, we are reluctant to utilize a test on employees unless we can explain the result and course of action required. Question 7C was confusing. It was not clear to us what measurements are envisioned in the category of allergic respiratory disease or contact dermatitis." (366, petroleum)

"Due to the great diversity of operations of this corporation, this questionnaire is not applicable." (371, no industrial code given)

"We do not engage in any form of biochemical genetic testing or cytogenetic testing. We are primarily a metal forming industry." (375)

"I have no questions about the above. As a physican who has been in full time occupational practice for 33 years I was amazed to read in the lay press that some union officials were alleging widespread use or plans for use of genetic testing by industry." (385, chemicals)

"To date we have not had the exposure, and therefore have not seen the need to do these tests." (305, Food)

"Attention John Gibbons: How can your organization afford Federal Express service from zip code 10001 to 10591 - 20 miles to the North of Manhattan. Signed, A Hard Working Taxpayer" (201, Food processing)

"Our employees are incidentally exposed to degreasers, solvents and non-lead based paints. We look to NIOSH to define areas where biochemical and other testing is prudent. We would discontinue use of any product which would exhibit qualities that would make such testing prudent however we would perform the testing of any of our employees so exposed." (207, fabricated metal products)

"This questionnaire is another example of wasting Federal tax monies. I would hope that Congress has more important business to conduct than the above questionnaire. Also there must be a more economic way to mail it than Federal Express overnight letter at $9.50." (231, Lumber and Paper mfg.)

"Biochemical genetic testing: If any thing should be done, it would be accomplished post-natally since appropriate family history would be available. Cytogenetic testing: would be appropriate in areas of exposure to potential chromosomal damaging agents (radation, chemicals, etc.)" (403, manufacturing and resale electricity)

"Is any industry doing this testing?" (118, Food)

"We have reviewed the current data on cytogenetic testing both in animals and in man and feel that these techniques are not yet applicable to standard medical surveillance of workers. It is recognized that the techniques may have potential value in risk assessment, and we hope that continued research work will better define that applicability. We feel strongly that current capabalities in the field do not allow the widespread use of these techniques at the present time." (121, manufacture of medical products for the health care industry, including both devices and drugs)

"-- Inc. was selected to participate in a survey conducted by NORC for the Office of Technology Assessment (OTA) of the U.S. Congress on the state of the art of genetic and cytogenetic testing programs. By error, we received a copy of the questionnaire to be completed by a union as well as a copy to be completed by a corporation.

I was concerned to note that the questionnaires were different in that questions no. 19 and 20 appearing on the union version of the form were absent from the corporation version. I am hopeful that any information you received from the union on these two questions will be deleted from the report to Congress since the data is obviously biased.

Many corporations have decided not to implement genetic and cytogenetic programs since the correlation of results of such testing with frank clinical diseases has not been demonstrated. This lack of predictability can lead to incorrect conclusions on the part of environmentalists and governmental agencies in assessing the risk of certain chemicals and substances.   does concur with the scientific literature which indicates that the proportion of occupational diseases attributable to genetic predisposition ranges from 10 to 20 per cent with diseases attributable to chromosomal aberrations ranging 1 to 5 per cent.

If you have any additional questions, please let me know." (   )

Appendix D

Background Frequencies for Chromosomal Aberrations

The data presented in table D-1 are not intended for direct comparisons of values obtained between laboratories; rather, they are meant to convey a sense of the range of normal background values for chromosomal aberrations reported in the literature.

The following abbreviations are used for culture media: D—Difco; E—Eagle's basal; G—Gibco; H—Ham's F10; M—McCoy's 5A; T—TC 199; and 1640—RPMI 1640.

The following abbreviations are used for aberrations: CTD—chromatid breaks; C—chromosome breaks; R—rings; D—dicentrics; E—exchanges; Cu—"unstable" aberrations, according to Buckton, et al.; Cs—"stable" aberrations, according to Buckton, et al.; AC—abnormal cells. All values are percentages. Gaps are not included, except where noted otherwise. In some cases it has been necessary to recalculate the original data.

A continuous line covering more than one complex aberration indicates that the aberrations were combined in the resulting frequency.

Table D-1.—Background Frequencies for Chromosomal Aberrations

Reference	Number of subjects	Number of cells	Culture medium	Culture time (hr)	CTD	C	R	D	E	Cu	Cs	AC
Legator and Hollaender, 1975	75	2,291	?	?	6.72	1.48	0	0.17	0.17	—	—	6.07
Lubs and Samuelson, 1967	10	3,720	T	68-72	5.9	1.0	0.22			—	—	8.3
Littlefield and Goh, 1973	31	29,709	T	72	—	3.0	0	0.12	0.32	—	—	6.0
Mattei, et al., 1979	1,084	15,754	?	72	4.6	1.7	0.71			—	—	~7.0
Aula and von Koskull, 1976	1,299	25,980	?	72	—	—	—	—	—	—	—	1.8
Ayme, et al., 1976	524	7,653	?	72	2.4	1.4	0.81			—	—	4.7
Husgafvel-Pursiainen, et al., 1980	52	5,200	T	50	—	—	—	—	—	—	—	1.3-1.8
A Review, 1975	134	~13,400	?	56	—	—	0.18		0.80	—	—	1.08
Awa, et al., 1971	79	~ 7,900			—	—	0.23		0.59	—	—	0.93
Honda, et al., 1969	10	1,000	?	46-50	2.7	0.4	0.1	0	0.1	0.4	0.2	~0.6[a]
Brandom, et al., 1978a	20	~ 2,000	M	~48	—	~0.7	~0.2			—	—	~0.9
Brandom, et al., 1978b	20	1,950	H	50 or 72	—	—	~0.2			—	—	~0.7
	68	7,406			—	—	0.65			—	—	~1.1
Brandom, et al., 1972	15	1,430	M	50 & 72	0.9	0.2	0	0	0	—	—	1.1
Lloyd, et al., 1972	316	23,200	E	48	—	—	—	0.078	—	—	—	—
Bauchinger, et al., 1980	11	12,700	H	48	—	—	0.02		—	—	—	—
Burgdorf, et al., 1977	44	?	T	72	—	—	—	—	—	—	—	0-3
Nordenson, et al., 1978	13	1,312	T	72	0.4	0.1	—	—	—	—	—	1.6
Tough and Brown, 1965	5	500	?	40-50	—	—	—	—	—	0.6	0.4	—
	38	~ 1,140			—	—	—	—	—	0.6	0.8	
Tough, et al., 1979	5	500	?	40-50	—	—	—	—	—	0.6	0.4	—
	6	600			—	—	—	—	—	1.67	0.5	—
	5	500			—	—	—	—	—	0.4	0.4	—
Forni, et al., 1971a	34	~ 3,400	?	68-70	—	—	—	—	—	0.49	0.04	—
Forni, et al., 1971b	34	~ 3,400	?	68-70	—	—	—	—	—	0.61	0.09	—
Picciano, 1979b	44	8,000	varied	72	1.1	0.35	0.06			—	—	1.4
Watanabe, et al., 1980	7	279	T	72	—	—	—	—	—	—	—	2.5
Kucerova, et al., 1977	35	5,054	?	56-58	0.97	0.28	—	—	0.18	—	—	1.37
Sram, et al., 1980	34	3,400	?	56-68	—	—	—	—	—	—	—	2.06
	21	2,100			—	—	—	—	—	—	—	1.33
Picciano, 1979a	75	15,000	varied	72	2.15	0.51	0.08			—	—	2.38
Mitelman, et al., 1980	18	3,600	?	72	1.6[b]		—	—		—	—	2.9
Shiraishi and Yosida, 1972	6	300	1640	72	—	—	—	—	—	—	—	~0.67
Deknudt, et al., 1973	5	1,800	H	45½	0.11	0.33	0			—	—	?
O'Riordan and Evans, 1974	31	3,100	H	45-48	4.46	0.42	—	—	—	—	—	?
Deknudt and Leonard, 1975	12	2,400	H	48	—	—	—	—	—	—	—	0.67
Bui, et al., 1975	4	356	?	48 & 72	—	—	—	—	—	—	—	6.0
	3	297			—	—	—	—	—	—	—	4.7

Table D-1.—Background Frequencies for Chromosomal Aberrations—Continued

Reference	Number of subjects	Number of cells	Culture medium	Culture time (hr)	CTD	C	R	D	E	Cu	Cs	AC
Bauchinger, et al., 1976	15	1,650	H	48	0.2	—	0.26			—	—	0.47
Forni, et al., 1976	11	1,075	T	68-70	—	—	—	—	—	—	—	4.88^{c}
Deknudt, et al., 1977	20	3,000	H	48	—	—	—	—	—	—	—	2.53^{c}
O'Riordan, et al., 1978	13	1,243	H	45-48	0.08	—	—	—	—	0.8	0.02	—
Forni, et al., 1980	12	1,130	T	48	—	—	—	—	—	0.08	—	—
Maki-Paakkanen, et al., 1981	12	1,200	?	?	—	—	—	—	—	—	—	2.0
Funes-Cravioto, et al.	42	4,200	T	72	—	—	—	—	—	—	—	4.76
Maki-Paakkanen, et al., 1980	16	3,200	?	72	—	—	—	—	—	—	—	2.4
Hogstedt, et al., 1981	15	1,500	T	50	—	—	—	—	—	—	—	1.6
Thiess, et al., 1981	21	2,100	T	70-72	—	—	—	—	—	—	—	1.4
Ducatman, et al., 1975	10	500	G	65-68	—	—	—	—	—	0.3	2.9	—
Purchase, et al., 1976	19	1,900	D	48 or 72	—	—	—	—	—	0.53	0.10	—
	5	500			—	—	—	—	—	0.50	0	—
Szentesi, et al., 1976	49	2,523	?	48	—	—	—	—	—	0.35	—	—
	44	2,988			—	—	—	—	—	0.56	—	—
Hansteen, et al., 1975	16	1,600	?	48	—	—	—	—	—	—	—	1.79
	32	3,200			—	—	—	—	—	—	—	2.33
Fleig and Thiess, 1978	20	2,000	?	?	—	—	—	—	—	—	—	2.1
Kucerova, et al., 1979	8	800	?	?	—	—	—	—	—	—	—	1.8
Anderson, et al., 1980	6	600	D	48 & 72					First sampling:	0.5	0	1.33
									Second sampling:	0.5	0	1.17
	8	800							First sampling:	0.75	0	1.0
		565							Second sampling:	0.13	0	0.38
Kirkland, et al., 1978	17	1,700	T	48	—	—	—	—	—	—	—	3.47
	19	1,900			—	—	—	—	—	—	—	2.47
Meretoja, et al., 1981	5	500	T	64-66	—	—	—	—	—	—	—	1.8
Hogstedt, et al., 1980	7	1,400	M	72	—	—	—	—	—	—	—	2.5
Bauchinger, 1981	22	11,000	H	48	—	0.16	0.05		0.09	—	—	—
Waksvik, et al., 1981	10	1,000	H	48	—	0.3	—	—	—	—	—	—
Verschaeve, et al., 1976	7	651	T	72	—	—	—	—	—	—	—	8.5
Thiess and Fleig, 1978	18	1,800	?	70-72	—	—	—	—	—	—	—	2.0
Cervenka and Thorn, 1974	10	1,594	T	72	—	—	—	—	—	—	—	1.38
Hook, et al., 1974	11	398	?	72	—	—	—	—	—	—	—	0.8
	4	288			—	—	—	—	—	—	—	1.4

[a] Excluding CTD and C.
[b] Includes only breaks and exchanges.
[c] Gaps included.

SOURCE: Office of Technology Assessment.

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Appendix E

Background Frequencies for Sister Chromatid Exchanges

These data are not intended for direct comparisons, but rather to convey a sense of the variability in the literature.

The following abbreviations are used for culture media: EB—Eagle' basal; G—Gibco 1A; H—Ham's F10; MEM—Delbecco's minimal essential medium; T—TC 199; and 1640.

Table E-1.—Background Frequencies for Sister Chromatid Exchanges

Reference	Number of subjects	Number of cells/subject	Culture medium	BudR (μg/ml)	SCE/cell
Carrano, et al., 1980	8	40-80	MEM	variable	7.59
Morgan and Crossen, 1977	50	20	H	10	7.9
Crossen, et al., 1977	20	20	G	10	6.37
Lambert, et al., 1978	14 smokers	≥20	?	100	16.2
	29 nonsmokers	—			13.1
Husgafvel-Pursiainen, et al., 1980	43 smokers	30	T	5	9.6
	40 nonsmokers				8.1
Goh, 1981	22 old	30	?	3	9.07
	23 young				8.05
Butler and Sanger, 1981	19	≥15	EB	6	8.4
Butler, 1981	32	≥20		6	8.1-8.7
Burgdorf, et al., 1977	44	∼15	T	30	5.8
Watanabe, et al., 1980	7	∼40	T	10	11.4
Mitelman, et al., 1980	18	20	?	?	8.7
Maki-Paakkanen, et al., 1981	12	30	?	5	9.8
Funes-Cravioto, et al.	15	20	T	?	13.5
	6				12.2
Hogstedt, et al., 1981	15	30	T	5	8.0
Garry, et al., 1979	12	20	MEM	4.5	5.98
Hansteen, et al., 1975	16	30	?	2	7.5
Kucerova, et al., 1979	8	50	?	?	9.41
Anderson, et al., 1981	6	30	1640	25	6.68
Kirkland, et al., 1981	14	varied	1640	150?	10.77
Bauchinger, et al., 1981	22	40	?	10	7.09
Waksvik, et al., 1981	10	30	?	5	6.5
Sorsa, et al., 1981	10	?	?	?	∼8.0

SOURCE: Office of Technology Assessment.

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Appendix F

Screening Tests (Available at Hospitals or Medical Centers) for Heritable Traits

G-6-PD deficiency

Numerous screening tests have been designed to identify the glucose-6-phosphate-dehydrogenase (G-6-PD) deficient erythrocytes. The most simple, reliable, and specific screening procedure is the fluorescent spot test (2). This procedure has been widely employed (4,9,13,15) and has been shown to be highly reliable in detecting the deficiency. It has also been automated and made available for widespread screening (3,14). Detection of G-6-PD levels lower than about 50 percent normal is achieved.

Sickle-cell trait

Several screening methodologies for sickle-cell abnormalities have been developed. The procedure consisting of cellulose-acetate electrophoresis (CAE) followed by solubility testing has been favorably regarded because of speed, cost, simplicity, accuracy, and ability to differentiate the various types of hemoglobin (1). Quantification of hemoglobin types is easily performed. In order to verify the electrophoresis procedure for HbS, any blood found to have HbS is subsequently evaluated via the solubility test as HbS displays abnormal solubility. CAE followed by a solubility test to confirm the presence of HbS has been the procedure recommended by the National Sickle Cell Disease Program and the National Hemoglobinopathy Standardization Laboratory at the Centers for Disease Control (11,12).

Thalassemias

Pearson, et al. (10) have developed an electronic measurement of mean corpuscular volume (MCV) which meets the requirements for a screening test for alpha and beta thalassemic heterozygotes. The procedure is rapid, automated, and inexpensive. It yielded no false negatives out of a study population of 300. However, it is possible that false positives may occur for persons with an iron-deficiency condition. Further, persons who are so-called "silent carriers" (exhibiting no clinical symptoms) of alpha or beta thalassemia cannot be detected by this screening test. The frequency of the silent carrier is thought to be uncommon for beta thalassemia.

NADH dehydrogenase deficiency

The definitive diagnosis of hereditary methemoglobinemia requires the demonstration of deficient NADH dehydrogenase activity in red cells. The Hegesh, et al. (6) assay is considered preferable because of its specificity, accuracy at low enzyme activity levels, and ease of operation.

Serum alpha$_1$-antitrypsin (SAT) deficiency

Several reliable, easily administered, and inexpensive tests have been developed for the screening of large populations for SAT deficiency. All of these tests are sensitive for the recessive homozygous condition, but only one of them (8) can reliably detect the intermediate heterozygous levels. The authors claim that this test is a practical screening procedure which could be applied in large scale.

Slow v. fast acetylation

Urine tests for detecting slow and fast acetylators have been developed in order to deal with the potential medical problem of slow acetylators being at enhanced risk of developing adverse reactions to isoniazid, an antitubercular treatment. The procedure is straightforward and simple, displaying an excellent capability to distinguish fast from slow acetylators (7).

HLA typing

The methodology for determining human leukocyte antigen types is considered simple and is frequently conducted in numerous medical centers in the United States. The typical cost is now less than $100 for a complete analysis (5).

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Appendix G

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Office of Technology Assessment

The Office of Technology Assessment (OTA) was created in 1972 as an analytical arm of Congress. OTA's basic function is to help legislative policymakers anticipate and plan for the consequences of technological changes and to examine the many ways, expected and unexpected, in which technology affects people's lives. The assessment of technology calls for exploration of the physical, biological, economic, social, and political impacts which can result from applications of scientific knowledge. OTA provides Congress with independent and timely information about the potential effects—both beneficial and harmful—of technological applications.

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